SUMMARY OF PROTOCOL CHANGES

Version # / Version Date: Amendment #8 / 23Nov2016

#	Page	Section	Comments
1	All	All	*Version date was updated on all pages.*
2	1	Version	Added Amendment #8 / 23Nov2016 *Rationale: Protocol Amendment #8 version is submitted to match the Updated Consent dated 23Nov2016 as suggested by CTEP*

No Changes made to Protocol with this Amendment

NCI Protocol #: 9460
Local Protocol #: PHL-091
Version # / Version Date: Initial / 24 July 2013
Amendment #1 / 15 Nov 2013
Amendment #2 / 06 Mar 2014
Amendment #3 / 24 Sep 2014
Amendment #4/ 20May2015
Amendment #5/ 29Jul2015
Amendment #6 / 05Nov2015
Amendment #7 / 15Apr2016
Amendment #8 / 23Nov2016

TITLE: A Phase 2 Study of Sequential Trametinib and GSK2141795 in Relapsed or Refractory Multiple Myeloma

Coordinating Center: Princess Margaret Phase II Consortium (PMHC)

Senior Scientific Investigator Dr. Amit Oza
Princess Margaret Hospital Phase II Consortium
Department of Medical Oncology
610 University Avenue, 5-700
Toronto, Ontario, CANADA
M5G 2M9
Tel: 416-946-2818
Fax: 416-946-2082
amit.oza@uhn.ca

Principal Investigator: Dr. Suzanne Trudel
Princess Margaret Cancer Centre
610 University Avenue, 10-721
Toronto, Ontario, CANADA
M5G 2M9
Tel: 416-946-4566
Fax: 416-946-2087
strudel@uhnres.utoronto.ca

Co-Investigators: Dr. Nizar Jacques Bahlis
Foothills Hospital
681-1403 29 Street NW
Calgary, Alberta, CANADA
T2N 2T9
Tel: 403-944-1564
Fax: 403-944-2102
NBahlis@UCalgary.ca

Dr. Christopher Venner

Cross Cancer Institute
11560 Unversity Avenue
Edmonton, Alberta, CANADA
T6G 1Z2
Tel: 780-432-8757
Fax: 780-432-8888
ChristopherPaul.Venner@albertahealthservices.ca

Dr. Annette Hay
Cancer Centre of Southeastern Ontario at Kingston General Hospital
25 King Street West
Kingston, Ontario, CANADA
K7L 5P9
Tel: 613-533-2946
Fax: 613-546-8219
Email: AHay@ctg.queensu.ca

Statistician:
Lisa Wang
Princess Margaret Cancer Centre
610 University Avenue, Toronto
M5G 2M9, Ontario, CANADA
Tel: 416-946-4501 ext. 4883
Fax: 416-946-2154
lisawang@uhnresearch.ca

Study Coordinator:
Smitha Udagani
Princess Margaret Cancer Centre
610 University Avenue, Toronto
M5G 2M9, Ontario, CANADA
Tel: 416-946-4501 ext. 3408
Fax: 416-946-2016
smitha.udagani@uhn.ca

Responsible Data Manager:
Chantale Blattler
Princess Margaret Cancer Centre
610 University Avenue, Toronto
M5G 2M9, Ontario, CANADA
Tel: 416-946-4501 ext. 3692
Fax: 416-946-2154
chantale.blattler@uhn.ca

NCI Supplied Agent(s):
Trametinib dimethyl sulfoxide (GSK1120212B), NSC# 763093
GSK2141795, NSC# 767034

SCHEMA

This is a multi-center, open-label, non-randomized, two stage, phase II study of trametinib in patients with relapsed or refractory multiple myeloma (MM). Bone marrow (BM) samples from patients will be analyzed for NRAS, KRAS, BRAF mutations at baseline visit. Patients will be stratified into one of two study groups:

- Biomarker positive (NRAS, KRAS, BRAF mutated as defined Appendix F)
- Biomarker negative (without NRAS, KRAS, BRAF mutation)

Patients will be independently recruited into either of the two groups based on biomarker positivity. All patients will receive trametinib 2 mg/day orally on a 28 day cycle. Patients who develop progressive disease on trametinib monotherapy or achieve less then a partial response (PR) after 4 cycles of treatment will have the option to continue on trametinib with the addition of GSK2141795. Progressive disease is defined by the IMWG, however in consultation with the Principle Investigator, GSK2141795 maybe added for progression not yet meeting the IMWG criteria if the treating physician feels that it is in the best interest of the patient. The dosing of trametinib and GSK2141795 will be according to the recommended 1.5 mg trametinib and 50 mg GSK2141795 daily dosing schedule. The M-protein level at the time of addition of GSK2141795 will be considered the new baseline, and the patients will be allowed to continue the new treatment schedule until further progression, toxicity, or patient/physician decision to discontinue.

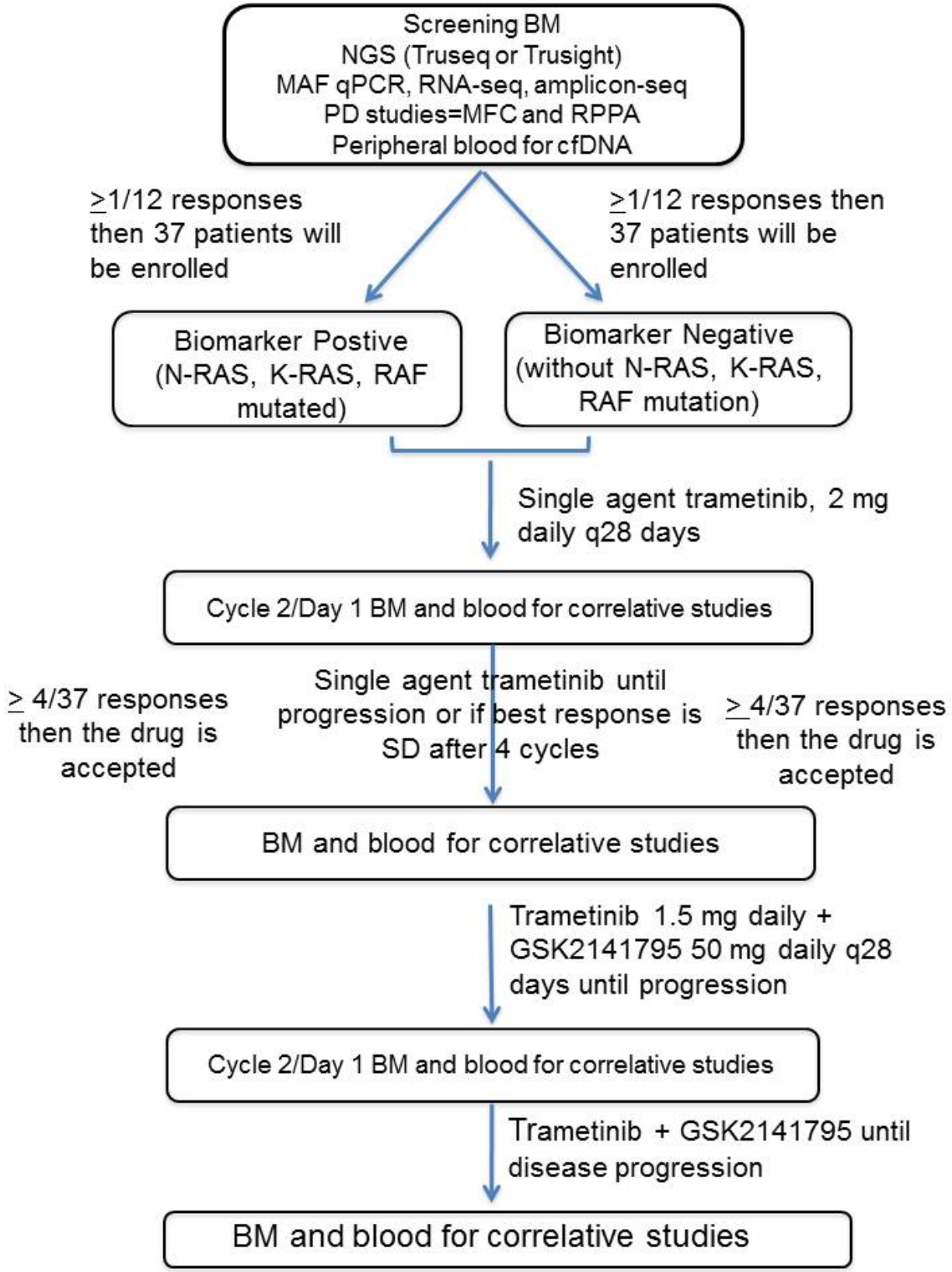
Screening BM
NGS (Truseq or Trusight)
MAF qPCR, RNA-seq, amplicon-seq
PD studies=MFC and RPPA
Peripheral blood for cfDNA
≥1/12 responses then 37 patients will be enrolled
≥1/12 responses then 37 patients will be enrolled
Biomarker Postive (N-RAS, K-RAS, RAF mutated)
Biomarker Negative (without N-RAS, K-RAS, RAF mutation)
Single agent trametinib, 2 mg daily q28 days
Cycle 2/Day 1 BM and blood for correlative studies
≥ 4/37 responses then the drug is accepted
Single agent trametinib until progression or if best response is SD after 4 cycles
≥ 4/37 responses then the drug is accepted
BM and blood for correlative studies
Trametinib 1.5 mg daily + GSK2141795 50 mg daily q28 days until progression
Cycle 2/Day 1 BM and blood for correlative studies
Trametinib + GSK2141795 until disease progression
BM and blood for correlative studies

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objectives

To evaluate the antitumor activity of trametinib determined by overall response rate (ORR) in patients that are stratified into groups based on:

- Biomarker positive (NRAS, KRAS, BRAF mutated as defined Appendix F)
- Biomarker negative (without NRAS, KRAS, BRAF mutation)

1.2 Secondary Objectives

- To evaluate progression free survival (PFS) and duration of response (DOR) in the two stratified groups
- To document ORR after the addition of GSK2141795 to trametinib in patients who have developed progressive disease or have achieved less then a partial response (PR) after 4 cycles of treatment
- To evaluate PFS and DOR in patients receiving trametinib plus GSK2141795
- To evaluate the safety profile of trametinib with and without GSK2141795

1.3 Exploratory Objectives

- To explore the relationship between clinical response and pharmacodynamic (PD) markers
- To explore the relationship between MAF expression as determined by quantitative PCR (qPCR), chromosomal abnormalities detected by florescence *in situ* hybridization (FISH), and clinical response
- To explore the role of integrin β7 as a biomarker of MAF expression
- To explore the relationship between objective clinical response as well as progressive disease and the tumor mutational profile
- To explore mechanism of PI3K/AKT and RAS-MEK-ERK activation and correlate these with clinical response and PD markers
- To explore the feasibility of extracting cfDNA from peripheral blood and detecting RAS and RAF mutations using cfDNA

2 BACKGROUND

2.1 Multiple Myeloma

Multiple myeloma (MM) is a mature B cell malignancy characterized by the latent expansion of malignant plasma cells in the bone marrow (BM). In the majority of cases, MM is epitomized by the hypersecretion of monoclonal immunoglobulin (Ig) molecules in the serum, which can be detected as a sharp peak (M-spike) by serum protein electrophoresis, or as Bence Jones proteins in the urine when Ig light chains are secreted. Among hematological malignancies, MM tumour cells are unique in their ability to cause significant bone destruction, which can in turn lead to osteoporosis and hypercalcemia. Together, the MM tumour, its products, and its effect on the surrounding environment, collectively contribute to the clinical manifestations of MM, which include persistent lytic bone disease, renal insufficiency, immune suppression and anemia (Dalton *et al.*, 2011; Rabb *et a.l*, 2009). On the molecular level, the malignant clonal plasma cells

can harbor numerical chromosomal abnormalities as well as translocation, some of which being of prognostic significance (Herve *et al.*, 2011; Munshi *et al.*, 2011).
Approximately 22,000 cases of MM are diagnosed each year in the United States (U.S.), with over 11,000 reported deaths due to MM annually (Howlader *et al.*, 2012). While the advent of autologous stem cell transplantation and advances novel biological agents have improved patient outcomes from a 3-year median life expectancy to 5 years, MM remains incurable (Dalton *et al.*, 2011; Rabb *et al.*, 2009). And though novel therapies in MM including the proteosome inhibitor, bortezomib and the immunomodulatory drugs, thalidomide and lenalidomide are highly effective and have improved survival of patients with relapsed MM, their administration is not curative, not all patients respond, and drug resistance eventually develops (Lauback *et al.,* 2009). Thus there remains a need for novel therapeutics approaches that target the underlying molecular and cellular mechanisms of disease and drug resistance. During the past decade, insights into the biology, genetics, and molecular pathology of the disease have provided a platform upon which novel therapeutic strategies that target the myeloma cells more specifically and effectively are being fashioned. One such target that has emerged is the RAS-MEK-ERK signaling pathway.

2.2 CTEP Agent(s)

2.2.1 Trametinib Dimethyl Sulfoxide (GSK1120212B)

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocates into the nucleus and phosphorylates a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival. Trametinib is one of the several MEK inhibitors in clinical development.

On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations as detected by an FDA-approved test (U.S. Food and Drug Amdinistration, 2013). On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test (U.S. Food and Drug Administration, 2014).

Experience to date indicates that MEK is a valid target. In a phase III trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival (Flaherty *et al.*, 2012). However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R) (Gopal *et al.,* 2010; Ebi *et al.,* 2011), PI3K/AKT inhibitors (Engelman *et al.,* 2008; Hoeflich *et al.,* 2009), and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria

for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported: Phase 1 AZD6244 + MK2206 (Tolcher *et al.,* 2011), phase 1 GDC-0973 + GDC-094 (MEK + PI3K inhibitor) (Bendell *et al.,* 2011).

2.2.1.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM) (Investigator's Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi *et al.,* 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin *et al.,* 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

2.2.1.2 Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)

There are 3 parts in this ongoing study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or

lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, NSCLC, CRC, or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The dose escalation part and some of the cohort expansion components have been completed. The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles (Infante *et al.,* 2010).

PK and metabolism of trametinib:
PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC_{0-24} and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for AUC_{0-24} across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak: trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean AUC_{0-24} was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half life and small peak: trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-drug interactions:
Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers:
The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma (Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity of Trametinib Monotherapy
In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD (2 mg/day continuously, or 2 mg for 21 days followed by a 1 week break). The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs) (Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic

cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). In the ITT analyses, the ORR was 22% in the trametinib group and 8% in the chemotherapy group; the median duration of PFS was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group; and the 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma

In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients (Borthakur et al., 2010). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

2.2.1.3 Safety Profile of Trametinib

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Due to limited experience in human subjects, there is currently incomplete information available about the relationship of AEs and administration of trametinib. Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest:
Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's Brochure, 2012a).

Rash: Rash was a common AE observed across different dose levels and in different

combinations (Investigator's Brochure, 2013). At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the ~370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were grades 1 or 2 (24% to 73%); 0% to 9% of patients experienced grade 3 rash AEs, and four patients had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea (Investigator's Brochure, 2013). Of ~320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders (Investigator's Brochure, 2013). Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (4% to 20% of all study patients); six patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

- *Retinal Pigment Epithelial Detachment (RPED):* Also known as chorioretinopathy, RPED is a visual impairment due to fluid accumulation under the retina and causes blurry vision. There were five cases of RPED, previously termed central serous retinopathy, reported from the integrated trametinib safety population consisting of subjects treated with trametinib 2 mg once daily from five studies (Investigator's Brochure, 2013). As of 23 June 2013, 14 cases of RPED were reported across the entire trametinib program amongst subjects treated with trametinib either as monotherapy or in combination with other anti-cancer agents (including cases from a MEK/BRAF combination study).

- *Retinal vein occlusion (RVO):* As of 23 June 2013, a total of four cases of RVO were reported across the entire trametinib program (including one case from a MEK/BRAF combination study) (Investigator's Brochure, 2013). All cases of RVO occurred in one eye only. Study drug was stopped at time of diagnosis in all cases. There was a decrease of visual acuity in two subjects with central RVO (CRVO) while the other two subjects had no meaningful decrease of visual acuity. In the two subjects with CRVO, local treatment with intravitreal injections of anti-VEGF antibodies was initiated within 2 weeks after RVO diagnosis, and visual acuity improved in one subject and restored to baseline conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with

administration of trametinib (Investigator's Brochure, 2013). However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96 total patients (including crossovers) with LFT changes, the majority were grade 1 or 2 in severity (4% to 20% of all study patients); 26 had grade 3 events, and 6 patients had grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs (Investigator's Brochure, 2013). Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2.0 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

In the phase 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Refer to dose modification guidelines for cardiac AEs in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis (Investigator's Brochure, 2013). Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had grade 1 or 2 pneumonitis and six subjects had grade 3 pneumonitis.

Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving

trametinib as compared to patients in the chemotherapy arm are listed as below:

Table: Selected adverse reactions (ARs) occurring in ≥10% of patients receiving trametinib AND at a higher incidence than in the chemotherapy arm (high in the trametinib arm compared with chemotherapy by ≥5% in overall incidence or by ≥2% grade 3 or 4 AEs)

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
Vascular disorders				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table: Percent-patient incidence of laboratory abnormalities occurring at a higher incidence in patients treated with trametinib versus chemotherapy (between-arm difference of ≥5% [all grades] or ≥2% [grades 3 or 4])

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

2.2.1.4 Clinical Experience with the Combination of Trametinib + Dabrafenib

Preliminary data on 45 patients participating in the phase 1/2 study of dabrafenib and trametinib, BRF113220, have been reported (Infante *et al.*, 2011).

PK
The plasma levels of dabrafenib were higher in combination with trametinib as compared to that with monotherapy. Geometric mean Day 15 AUC of dabrafenib in combination ranged from 3539 to 5187 ng•hr/mL, and the AUC observed in the monotherapy study was 2619 ng•hr/mL. Further data are required to understand this difference.

PK of trametinib did not appear to be affected by the addition of dabrafenib. Preliminary results showed that the geometric mean dose-normalized $AUC_{0-\tau}$ (CV%) for trametinib (dose normalized for the 2.0 mg QD dose) in combination with dabrafenib at 150 mg BID was 302 ng•hr/mL (n=17; 35%) on Day 15. Historical PK data from the trametinib FTIH study (MEK111054) indicated a mean Day 15 $AUC_{0-\tau}$ (CV%) of 360 ng•hr/mL (31%).

Safety and the RP2D for the combination of Trametinib and Dabrafenib
One DLT of a recurrent grade 2 neutrophilic panniculitis occurred, and pyrexia was common (51%). The RP2D was 150 mg BID dabrafenib plus 2 mg QD trametinib (both agents at the RP2D for single agent). Of the 137 patients enrolled, 32 patients were treated at the RP2D. SAEs experienced by more than one patient include: pyrexia (5%), hypotension (4%), nausea (3%), and 2% of patients had a constellation of AEs including vomiting, dehydration, or renal failure. The only grade 4 AE was a sepsis-like syndrome with fever/hypotension. Grade 3 AEs included generalized rash (n=2, 4%) and neutropenia (n=2, 4%). Skin toxicity (rash) occurred in 9 (20%) patients. Of note, the rate of SCC was 2% in this study. A single case of grade 5 hyponatremia was reported. Other common AEs are listed in the table below.

Summary of selected AEs experienced by ≥5% of patients regardless of causality in BRF113220 (treated at RP2D)

AE Term	Dose Escalation Cohort (150mg BID/2 mg QD) (n=31)
Any AE, n (%)	24 (77)
Pyrexia	10 (32)
Rash	4 (13)
Dermatitis acneiform	1 (3)
Hypotension	4 (13)

Activity
Among 77 evaluable patients with melanoma who had not received prior BRAF inhibitors, there were 43 responses (56%), including 4 CRs (5%) and 39 PRs (51%) (Weber *et al.*, 2012). Twenty-nine patients experienced SD, and three patients experienced PD. Patients were treated on four escalating dose levels of dabrafenib/trametinib (mg BID/mg QD): 75/1, 150/1, 150/1.5, 150/2. The confirmed RR for each dose level, respectively, was 67% (n=6), 64% (n=22), 48%

(n=25), and 54% (n=24). Median PFS (months) for each of the first three dose levels, respectively, was 8.7, 8.3, and 5.5; PFS data are not mature for the fourth (150/2) dose level. Overall PFS was 7.4 months.

Currently, the randomized phase 2 portion (Part C) of the study of dabrafenib with or without trametinib has enrolled 162 patients as of September 1, 2011 (Investigator's Brochure, 2012b).

2.2.1.5 Clinical Experience with the Combination of Trametinib + GSK2141795 (AKT inhibitor) (TAC113886)

Twenty-three patients with advanced solid tumors received the combination using a zone-based escalation procedure enabling evaluation of multiple combination doses in parallel cohorts (Kurzrock *et al.,* 2011). While the RP2D for single agent for single agent trametinib and GSK2141795 are 2 mg/d and 75 mg/d, dose reductions were required for the combination. DLTs include grade 2 AST and ALT elevation, and grade 3 chest pain with sustained ventricular tachycardia; all DLTs were reversible with drug interruption. The most common AEs (≥10%) included nausea (26%), AST elevation (22%; grade 3/4, 9%), fatigue (22%) and rash (22%). Three MTDs were defined for variable dose ratios: 2 mg trametinib + 25 mg GSK2141795; 0.5 mg trametinib + 75 mg GSK2141795; and 1.5 mg trametinib + 50 mg GSK2141795. Three of 13 evaluable patients (unselected) had tumor shrinkage of 8% (ovarian), 16% (endometrial), and 17% (ovarian) after 8 weeks on study. The dose regime of 1.5 mg trametinib + 50 mg GSK2141795 will be considered for further development. Additional trials to explore alternate schedules (*e.g.*, intermittent) and pharmacodynamic markers are ongoing.

2.2.2 GSK2141795

GSK2141795 is an ATP competitive pan-AKT inhibitor. AKT, a serine/threonine protein kinase with three isoforms, is active in several pathways that regulate survival, proliferation, tissue invasion and metabolism. Since AKT-mediated pathways are important in tumor proliferation and survival, AKT kinases are promising targets for therapeutic intervention. Hyperactivation of the AKT pathway can also correlate with chemotherapy resistance and poorer prognosis.

Unless otherwise specified, information provided herein regards AKT inhibitor GSK2141795 dosed as a single agent. Information on the combination of GSK2141795 and MEK inhibitor trametinib can be found 2.2.1.5.

Pharmacokinetics (PK)
Single-dose (Day 1) PK parameters of GSK2141795 were evaluated in the first-time-in-human (FTIH) study (PCS112689). Preliminary data indicated that plasma concentrations for GSK2141795 were measurable for all subjects over the 72 hours after a single dose over the dose range tested (10 mg to 150 mg). In addition, drug concentrations were measurable on Day 8, suggesting that GSK2141795 can still be found in the plasma at least 1 week after a single dose of study drug over the dose range tested (75 mg to 100 mg). While the exposure for the 100 mg and 150 mg doses were similar following a single dose, drug exposure following multiple doses was approximately in proportion to dose. GSK2141795 accumulated 2.5- to 8.4-fold with repeat daily dosing. Mean area under the concentration-time curve [$AUC_{(0-24)}$] and maximum plasma

concentration (C_{max}) values generally increased in a dose-proportional manner, although there was variability among subjects. Median time to reach peak concentration (T_{max}) across doses was 3 hours and ranged from 0 to 4 hours. The mean value for the effective half-life of elimination ($t_{½}$, eff), across subjects was 3.0 days and ranged from approximately 1.3 to 5.5 days.

Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)
The MTD of single-agent GSK2141795 is 75 mg once-daily as determined by the FTIH study. The RP2D of single-agent GSK2141795 has not been determined.

Potential Drug-drug Interactions
In vitro data indicate that GSK2141795 is a CYP3A4 substrate. Drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and should either be prohibited or used with caution. Drugs that are strong inducers of CYP3A and may result in lower exposures of GSK2141795 should also be prohibited. GSK2141795 also appears to be a moderate in vitro inhibitor of CYP2C8 (50% inhibitory concentration [IC_{50}] 3 mcM) and CYP3A4 (IC_{50} 11 mcM). Drugs that are substrates of CYP3A4 or CYP2C8 with a narrow therapeutic index may be prohibited. Drugs that are sensitive substrates of CYP3A4 or CYP2C8 should be used with caution.

The following medications (including but not limited to) are prohibited during the study:

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/BCRP/CYP3A4 substrates since concentrations of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
cisapride	Hypnotics and Sedatives
pimozide	Antidepressant, Antipsychotics, Antianxiety agents
astemizole	Antihistamine
BCRP Substrate	**Therapeutic Area**
rosuvastatin,sulfasalazine	HMG-CoA Reductase Inhibitors, gastrointestinal agents
PROHIBITED – strong inducers/inhibitors of CYP3A4	
Strong CYP3A4 Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (*e.g.*, rifampin, rifabutin, rifapentine), troleandomycin	Antibiotics
itraconazole, ketoconazole	Antifungals
nefazodone	Antidepressants
atazanzvir, delaviridine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, nevirapine	Antivirals
carbamazepine, phenobarbital, phenytoin	Anticonvulsants

For a list of medications that may alter the concentrations of trametinib or GSK2141795 or have their elimination altered by trametinib or GSK2141795 and thus should be administered WITH

CAUTION is provided in section 5.2.3.

GSK2141795 Safety Profile and Management
Based on available adverse event (AE) data from 151 subjects dosed as of the data cut-off date of May 6, 2012, the most common toxicities of GSK2141795 monotherapy or in combination with trametinib are gastrointestinal (GI)-related (diarrhea, nausea, and vomiting) and fatigue (Investigator's Brochure, 2012). Hyperglycemia, hypoglycemia, mucositis, and rash are also commonly observed. In addition, three cases of hypothyroidism have been noted.

GI-related AEs
Interim medical history, continuous assessment of AEs, physical examination, and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to standard medical practice. Treatment will be discontinued for clinically significant toxicity.

Diarrhea: This is the most frequent drug-related AE in patients receiving GSK2141795. Most diarrhea events reported were Grade 1 and 2. Based on current data, the majority of cases of diarrhea occur within the first 3 to 4 weeks of starting the drug. In most cases, diarrhea resolves with interruption of GSK2141795 dosing and implementation of supportive treatment. Based on preliminary data, re-challenge with a reduced dose of GSK2141795 is tolerated. Early diarrhea management for subjects taking GSK2141795 is critical and must be initiated as soon as the first episode of diarrhea has occurred. Supportive care interventions should include dietary modifications, anti-diarrheal medications, and supplementary intravenous hydration as needed.

Mucosal inflammation: Mucositis has been observed as a dose-limiting toxicity (DLT).

Early intervention for signs and symptoms of mucosal inflammation is recommended and encouraged. Based on preliminary data, dose interruption followed by dose reduction on re-challenge can ameliorate symptoms. Supportive care interventions should include good oral hygiene, adequate pain control, prevention of superinfection, and maintenance of adequate of hydration with supplementary intravenous hydration as needed.

Cutaneous AEs
Rash may or may not be associated with pruritis. Preliminary data suggest that drug interruption and dose reduction upon re-challenge ameliorate the symptoms. Rash management should focus on symptom relief and maintenance of an intact integument. Dermatology consult is recommended when clinically appropriate. Topical steroid creams have been found to provide some relief from symptoms. Treatment will be dose reduced or discontinued for clinically significant toxicity not adequately controlled by supportive care measures.

Glucose Abnormalities
Hyperglycemia: Hyperglycemia occurred in patients receiving ≥75 mg/day with the majority of events occurring at doses exceeding the maximum tolerated dose (MTD) of 75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg, 100 mg, and 150 mg daily doses. The frequency and severity of hyperglycemia AEs is reduced at the 75mg/day dose as compared with higher doses. It is not clear if oral anti-hyperglycemic drugs are useful to

ameliorate the hyperglycemia, although both intravenous and sliding scale insulin have been helpful.

To reduce the risk of hyperglycemia, patients with abnormal fasting glucose values at screening will be excluded. In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with regular hemoglobin A1C (HbA1C) ≤8% at screening. Patients will have glucose and insulin monitored during the study. If hyperglycemia is observed, supportive therapy will be provided according to standard medical practice. Treatment will be dose reduced or discontinued for clinically significant toxicity that cannot be adequately managed medically.

Hypoglycemia: Asymptomatic hypoglycemia occurred in patients receiving ≥75 mg/day. Treatment-related grade 3 or grade 4 events were observed at 75 mg and 100 mg daily doses. The mechanism of hypoglycemia is currently unknown. Careful monitoring of glucose levels and encouragement of adequate oral intake are recommended.

Thyroid Events
Reversible minimal to mild hypertrophy of follicular cells was seen in the thyroid glands of dogs given 5 mg/kg/day for 4 weeks. The relationship to GSK2141795 and clinical significance are unknown, although three cases of drug-related hypothyroidism have been reported. Continued monitoring for thyroid function (thyroid-stimulating hormone laboratory testing) will be incorporated in all clinical protocols. Supportive therapy will be provided according to standard medical practice, and treatment will be discontinued if necessary.

Other Glandular Events
In both rats and dogs, several glandular structures (salivary, nasal, mammary, and Brunner's glands) had reversible reductions in secretory content and/or apoptosis of individual acinar cells. The mechanism for this finding is not understood, although it may result in dry mouth, a toxicity that has been reported in some patients. Frequent monitoring with medical history, physical examination, and clinical laboratory assessments will be done. If clinically significant toxicity is observed, supportive therapy will be provided according to standard medical practice, and treatment will be discontinued if necessary.

2.3 Rationale

There is substantial evidence validating the importance of RAF and MEK in cancer progression and in promoting cancer growth. Mutationally activated BRAF and RAS have been identified at high frequency in a variety of human cancers including MM (Santarpia *et al.*, 2012; McCubrey *et al.*, 1994). Further germline de novo mutational activation of HRAS, KRAS, BRAF and MEK1/2 have been found in patients with developmental disorders that have an increased incidence of cancers (Tartaglia et *al.*, 2011). Both constitutively activated RAS and RAF kinases are known to potently transform mouse fibroblast and inhibition of the downstream effectors, MEK or ERK are required for the transforming activities of RAS (McCubrey *et al.*, 1994). As a result, considerable effort has been devoted to the development of cancer drugs directed against the RAS-MEK-ERK pathway.

In addition to its well-documented role in solid tumors, many studies have highlighted the ability

of the RAS-MEK-ERK pathway to stimulate the proliferation and induce chemoresistance of MM cells. Activating mutations of KRAS, NRAS and BRAF have been reported in approximate 27%, 24% and 4%, respectively of MM cases (Chapman *et al.,* 2012; Morgan *et al.,* 2012). RAS mutations are implicated in disease progression from MGUS to overt MM, aggressive phenotype and shorter survival (Corradini *et al.,* 1994; Weiss *et al.,* 2010). Studies in myeloma cell line models demonstrate that ectopic expression of mutated RAS can confer cytokine independent growth, induces proliferation and resistant to certain chemotherapeutic drugs such as dexamethasone and doxorubicin (Billadeau *et al.,* 1995; Rowley *et al.,* 2002). Further in MM patients that harbor the t(4;14) translocation or translocations that dysregulate the MAF family of transcription factors (approximately 30% of MM patients) the MEK-ERK pathway appears to regulate expression of MAF and inhibition of MEK selectively induces apoptosis of MAF-expressing myeloma tumors (Annunziata *et al.,* 2011). These studies suggest that targeting the RAS-ERK-MEK pathway may be a valuable approach to treatment of MM and that MEK inhibitors may preferentially benefit patients whose tumors harbour mutations of RAS, RAF or overexpress MAF proteins.

As MEK is a critical node in the RAS-MEK-ERK signaling pathway it represents an attractive focus for the development of novel targeted therapy potentially benefiting a large proportion of cancer patients whose tumors depend on this pathway. Experience to date indicates that MEK is valid therapeutic target. Single agent clinical activity has been reported in BRAF mutated melanoma, cholangiocarcinoma, and MM ((Flaherty *et al.,* 2012; Bekaii-Saab *et al.,* 2011; Zingone *et al.,* 2011). In a phase II study of the MEK inhibitor, AZD6244 an intermin analysis reported 2 objective responses and 12 stable diseases were reported in 25 evaluable relapsed myeloma patients (Holkova *et al.*, 2011). Interestingly, of the two responders one had a translocation t(4;14) and the other expressed MAF-B (Zingone *et al.,* 2011). Although preclinical and clinical data suggest that cells with BRAF or RAS mutations are more likely to respond to MEK inhibitors, the response rate is low. Potential explanations include the intrinsic or induced activation of alternative signaling pathways and in particular the PI3K/AKT signaling. In myeloma tumors, the PI3K pathway is not frequently mutated however phosphorylated AKT, which is indicative of PI3K activity, is detected in approximately 50% of cases (Zöllinger *et al.,* 2008). Interestingly, DEPTOR a positive regulator of the PI3K pathway is upregulated, especially in cases of MAF-positive MM (Peterson *et al.,* 2009). Pre-clinical studies suggest that AKT activation in MM tumors is independent of oncogenic RAS and that combined inhibition of RAS and AKT strongly enhances MM cell death Steinbrunn *et al.,* 2011). The data suggests that additionally targeting the AKT pathway may increase MEK inhibitor response rates.

These studies provide the rationale for targeting MEK with trametinib in myeloma. The pre-clinical data supports the evaluation of MEK inhibitors in patients as a single-agent and in combination with an AKT inhibitor in MM for patients who fail to respond to MEK inhibition alone. The data also support the stratification of patients based on NRAS, KRAS, and BRAF mutational status and potentially MAF expression, factors that we hypothesize will influence response. Trametinib will be evaluated as single agent in a Phase II trial. GSK2141795 (AKT inhibitor) will be combined with trametinib for patients progress on treatment or who fail to respond to trametinib after 4 cycles of treatment. This period of time is anticipated to provide a reasonable estimate of the response to single-agent trametinib, as the median time to response for two active agents studied in previously conducted phase III trials (bortezomib and

lenalidomide/dexamethasone) estimated this to be 42 days (Richardson *et al*., 2005) and 2.1 months (Dimpoulos *et al*., 2007). Indeed in the ECOG study of low dose vs high dose dexamethasone in combination with lenalidomide, only 5 patients of 445 upgraded their response to a partial remission after 4 cycles of treatment (Rajkumar *et al*., 2010). It is understood that given the addition of the AKTi after 4 cycles for patients who fail to achieve a PR or better, this trial will only provide an estimate of the overall response rate to single agent trametinib.

2.4 Correlative Studies Background

Our hypothesis is that a MEK inhibitors evaluated in the context of a Phase II trial will induce clinical responses in a subset of myeloma patients and that biological correlates obtained from serial bone marrow (BM) sampling will provide insights into patient selection biomarkers and mechanisms of resistance.

Next-generation sequencing analysis (NGS) : Our hypothesis is that patients whose tumors harbor mutations of RAS or RAF will preferentially respond to MEK inhibition. To test this hypothesis and to potentially enhance the effect size we have chosen to stratify patients based on the presence or absence of mutations of RAS or RAF. Mutational analysis will be performed by the University Health Network (UHN) CLIA laboratory. . Cases that are positive for mutations of RAS or RAF and an allele fraction of $\geq$10% will be stratified to the biomarker positive group.

MAF expression: Pre-clinical studies demonstrate selective induction of apoptosis of MAF-expressing myeloma tumors suggesting that this group of myeloma patients may preferentially respond to MEK inhibitors. RNA derived from screening BM samples will be used to quantify MAF expression (c-maf, MAF-B and MAF-A) by quantitative PCR (qPCR). As this assay has not been validated, results will not be used to stratify patients; however, clinical response rates will be correlated with MAF expression as an exploratory endpoint. In additon, the relationship between MAF expression and chromosomal abnormalities will be evaluated by qPCR and florescence *in situ* hybridization (FISH). FISH is a standard molecular assay performed in cases of multiple myeloma. Evidence suggests that high levels of MAF occur in myeloma tumors with translocations t(14:16) that dysregulates cMAF, t(14:20) that dyregulates MAFB, and t(4;14) that results in overexpression of FGFR3 and MMSET (Annunziata *et al*., 2011). As an exploratory endpoint we will therefore determine the correlation between these two molecular assays (qPCR and FISH). We propose that this will provide information for better clinical interpretation of an assay that is already employed as standard of care for multiple myeloma.

Integrin-β7 expression: Integrin-β7 is cell surface protein whose expression is regulated by the transcription factor MAF (Hurt et al., 2004). Its cell surface expression can be detected by flow cytometry making integrin-β7 a potential biomarker that can easily translate to the clinical lab. As an exploratory endpoint we will measure integrin-β7 on CD138+ myeloma cells and correlate positivity with MAF expression and clinical responses.

Pharmacodynamic (PD) Studies

Multi-parameter Flow Cytometry (MFC) Studies: Myeloma cells will be evaluated for target modulation and the effects of trametinib with or without GSK2141795 on downstream signaling targets of RAS signaling and alternative pathways (PI3K/AKT). With the recent introduction of

techniques that measure the activation states of signaling pathways using phosphospecific antibodies, the scope of MFC now extends into molecular therapeutic monitoring in the clinic (Tong et al., 2006). By using MFC applications, we will determine whether the MEK target ERK, is activated in myeloma cells pre-treatment and whether administration of trametinib inhibits ERK phosphorylation in primary MM cells. Further, we will determine whether at progression, ERK phosphorylation remains suppressed despite trametinib treatment providing valuable insights into whether escape mechanisms are ERK-independent or ERK-dependent. In addition, we will evaluate whether the PI3K/AKT pathway is activated at baseline or is induced in response to single agent trametinib or at progression, as a potential mechanism of resistance. The results will be correlated to response to trametinib +/- GSK2141795 and analyzed as an exploratory endpoint.

Reversal Phase Protein Arrays (RPPA): RPPA is a quantitative assay that analyzes nanolitre of sample for potentially hundreds of proteins (Iadevaia et al., 2010). This antibody-based assay determines levels of protein expression, as well as protein modifications such as phosphorylation. RPPA allows concordant interrogation of multiple signaling molecules and their functional status. The integrated information has the potential to display the functional outcomes affected by therapeutics that may inform on predictors of response or mechanisms of resistance.

The products of these correlative assays are to validate biomarkers related to MM responses and outcomes to MEK inhibitors that will serve to guide patient selection strategies for subsequent clinical trials. In addition, we expect to begin testing hypotheses around novel biomarkers and mechanisms of resistance that may inform combination strategies and guide the development of innovative, personalized therapeutics for MM and cancers and general.

RAS and BRAF mutation detection using circulating free DNA (cfDNA)
Currently the detection of RAS and BRAF mutations is carried out in tumor tissue by NGS. This requires bone marrow aspiration for derivation of tumor tissue and CD138 purification of myeloma tumor cells for DNA extraction. Recent studies have validated the detection of KRAS and BRAF mutations from circulating free tumor DNA (cfDNA). cfDNA was detected in 100% of patients with metastatic colorectal cancer and showed 100% specificity and sensitivity for BRAFV600E mutation and 98% specificity and 92% sensitivity for KRAS mutations (*Thierry AR et al. 2014*). Thus this represents a minimally invasive and cost-effective method for identification of patients that are most likely to benefit from targeted therapy. We postulate that patients with MM will similarly have detectable cfDNA and that mutations of RAS and RAF can be efficiently and effectively detected from cfDNA.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed Multiple Myeloma NOS (10028566).

3.1.2 Patients must have measurable disease as defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of protocol therapy):

- Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
- Urine M-protein ≥ 200 mg/24 h
- Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
- Biopsy proven plasmacytoma (should be measured within 28 days of first study drug administration). Prior biopsy is acceptable.
- If the serum protein electrophoresis is unreliable for routine M-protein measurement, quantitative immunoglobulin levels on nephrolometry or turbidometry will be followed.

3.1.3 A diagnosis of MM and documentation of relapsed or relapse/refractory status following at least 2 prior lines of therapy.

3.1.4 Documented lab results confirming tumor mutational status (as outlined in Appendix F, Table 3) must be obtained at screening. Patients in whom mutational status cannot be determined will be deemed ineligible.

3.1.5 Because no dosing or adverse event data are currently available on the use of trametinib with and without GSK2141795 in patients <18 years of age, children are excluded from this study.

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.7 Life expectancy of greater than 6 months.

3.1.8 Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

3.1.9 All prior treatment-related toxicities must be CTCAE v4 grade ≤1 (**except alopecia**) at the time of registration. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae are permitted to enroll.

3.1.10 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) ≥ 1.0 x10^9/L
- Hemoglobin ≥ 8 g/dL
- Platelets ≥ 50x10^9/L
- Albumin ≥ 2.5 g/dL
- Total bilirubin ≤ 1.5x institutional ULN (isolated bilirubin > 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
- Aspartate aminostransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5x institutional ULN

- Serum creatinine ≤ 1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥ 30 mL/min *OR* 24-hour urine creatinine clearance ≥ 30 mL/min
- Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5x institutional ULN
- Fasting serum glucose < 126 mg/dl (7 mmol/l)
- Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal (LLN) by ECHO or MUGA

3.1.11 Subjects that have been previously diagnosed with Type 2 diabetes or steroid-induced diabetes must also meet the additional following criteria:

- Diagnosed with diabetes ≥ 6 months prior to enrolment
- HbA1C ≤ 8% at screening visit

3.1.12 The effects of trametinib *or* GSK2141795 on the developing human fetus are unknown. For this reason and because MEK inhibitors as well as other therapeutic agents used are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to the start of protocol therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of trametinib administration.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 History of another malignancy.
Exception: Patients who have been disease-free for 3 years, or patients with a history of completely resected non-melanoma skin cancer and/or patients with indolent second malignancies, are eligible. Consult the CTEP Medical Monitor if unsure whether second malignancies meet the requirements specified above.

3.2.2 History of interstitial lung disease or pneumonitis.

3.2.3 Diabetes mellitus currently requiring insulin. Subjects with a history of steroid-induced hyperglycemia may be enrolled provided that HbA1C at screening visit is ≤ 8%.

3.2.4 Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 28 days prior to randomization and/or daily or weekly chemotherapy or other approved anti-myeloma therapy without the potential for delayed toxicity within 14 days prior to registration.

3.2.5 Use of other investigational drugs within 28 days preceding the first dose of trametinib and during the study.

3.2.6 Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

3.2.7 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trametinib or excipients or to dimethyl sulfoxide (DMSO) or GSK214795.

3.2.8 Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study treatment. (note: megestrol [Megace] if used as an appetite stimulant is allowed).
- Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

3.2.9 *In vitro* data indicate that GSK2141795 is a CYP3A4 substrate. Drugs that potently inhibit CYP3A4 could lead to increased GSK2141795 exposure in subjects, and should either be prohibited or used with caution. Drugs which are strong inducers of CYP3A and may result in lower exposures of GSK2141795 should also be prohibited. GSK2141795 also appears to be a moderate *in vitro* inhibitor of CYP2C8 (50% inhibitory concentration [IC_{50}] 3 mcM) and CYP3A4 (IC_{50} 11 mcM). Drugs that are substrates of CYP3A4 or CYP2C8 with a narrow therapeutic index may be prohibited. Drugs that are sensitive substrates of CYP3A4 or CYP2C8 should be used with caution. (Refer to 5.2.3)

3.2.10 History or current evidence/risk of retinal vein occlusion (RVO) or Retinal Pigment Epithelial Detachment (RPED):

- History of RVO or RPED, or predisposing factors to RVO or RPED(*e.g.*, uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
- Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO or RPED such as evidence of new optic disc cupping, evidence of new visual field defects, and intraocular pressure >21 mm Hg.

3.2.11 History or evidence of cardiovascular risk including any of the following:

- LVEF<LLN.
- A QT interval corrected for heart rate using the Bazett's formula QTcB ≥480 msec (≥ 500 msec for subjects with bundle branch block)
- History or evidence of current clinically significant uncontrolled arrhythmias (exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible).
- Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
- Subject with intra-cardiac defribillators or pacemakers.
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
- History or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system
- Treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.
- Known cardiac metastases.

3.2.12 Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection, which will be allowed).

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 Animal reproductive studies have not been conducted with trametinib. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception. If a female patient or a female partner of a patient becomes pregnant while the patient receives trametinib, the potential hazard to the fetus should be explained to the patient and partner (as applicable). These potential risks may also apply to GSK2141795.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse and the proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

The population demographics and distribution of minorities in Canada is included in the following table:

Table: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		Alberta		Ontario		Nova Scotia		Total	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20%	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13%**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22%	329,925	11%	2,153,045	19%	34,525	4%	3,353,936	**18%**

Source: Statistics Canada, Census of Population.

Data from our consortium has been compiled regarding the representation of minorities on previous clinical trials, and the distribution is as follows:

Population Percentage of Minority and Gender of entering PMHC Trials			
	2010	2011	2012
Visible Minorities			
Black	0.9	2.3	1.2
Asian	10.1	10.9	11.6
Hispanic	10.1	2.3	3.5
Total	**21.1**	**15.5**	**16.3**
Women	**59.6**	**56.6**	**44.2**

4 REGISTRATION PROCEDURES

4.1 General Guidelines

The Study Coordinator at the Princess Margaret Consortium Central Office will enter eligible patients on study centrally. All sites should call the Study Coordinator (listed on cover page) to verify biomarker cohort availabilities. The required forms (Eligibility Checklist) will be provided upon site activation.

Following registration, patients should begin protocol treatment within 3 days. Issues that would cause treatment delays should be discussed with the Principal Investigator (cc the central office study coordinator). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified

of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. A participating site may order agents only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.2 Registration Process

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the PMH Phase II Consortium Central Office. The eligibility checklist will only be sent once this has been received.

No patient can receive protocol treatment until registration with the Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Central Office prior to registration.

To register a patient, the following documents are to be completed by the research nurse or data manager and sent / faxed to the Central Office Study Coordinator:
- Signed patient consent form
- Eligibility Checklist CRF signed by the investigator

To complete the registration process, central office will review the checklist and once eligibility has been confirmed:
- Assign a patient study number
- Assign the patient a dose
- Register the patient on the study
- Fax or e-mail the confirmation worksheet with the patient study number and dose to the participating site

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the study coordinator listed on the front sheet. Patient registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the central office will be closed.

5 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an *outpatient* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.1. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will receive trametinib 2 mg taken orally once a day continuously of a 28 day cycle. Patients who develop progressive disease on trametinib monotherapy or achieve less then a PR

after 4 cycles of treatment will have the option to continue on trametinib with the addition of GSK2141795. Progressive disease is defined by the IMWG, however in consultation with the Principle Investigator, GSK2141795 maybe added for progression not yet meeting the IMWG criteria if the treating physician feels that it is in the best interest of the patient. The dosing of trametinib and GSK2141795 will be according to the recommended 1.5 mg trametinib and 50 mg GSK2141795 daily dosing schedule. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course**:**

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Trametinib	Empty stomach; 1hr before or 2hr after a meal	2mg alone OR 1.5mg in combination with GSK2141795	oral	daily	28 days
GSK2141795	Empty stomach 1 hour after a small snack and 2 hours before a meal	50mg	oral	daily	
**Doses as appropriate for assigned dose level; refer to section 6.1. Please refer to Appendix E for example drug administration regimen of combination treatment					

For patients in whom the trametinib dose during monotherapy has been reduced to 1.5 mg the dose of trametinib will not be further reduced upon the addition of GSK2141795. For patients on trametinib monotherapy who have been dose reduced to 1.0 mg, their dose will remain at 1.0 mg upon the addition of GSK2141795. No dose re-escalation is permitted in the study (except for in the events defined in section 6).

5.1.1 Trametinib

The effect of food on trametinib absorption is unknown. The current recommendation is to administer trametinib on an empty stomach, either 1 hr before or 2 hr after a meal; the recommendation to administer trametinib fasting may change based on emerging data.

5.1.2 Other Agent(s) GSK2141795

Capsules must be taken fasting 1 hour following a meal and 2 hours before the next meal. Based on nonclinical data and increasing clinical experience, it is possible that GSK2141795 may be a direct gastrointestinal mucosal irritant such that subjects with GI dysmotility or GERD may be predisposed to symptoms of dyspepsia. Therefore, in an effort to decrease this discomfort, we have the following recommendations. The following is recommended:

- Eat a small snack followed by 60 minutes of fasting prior to taking GSK2141795. Water is allowed during this fasting period.

- If possible, take each GSK2141795 capsule approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz).
- Remain upright for 30 minutes after taking the last capsule of GSK2141795.
- Fast for 2 hours after ingestion of the last capsule of GSK2141795. Water is allowed during this fasting period.
- In more severe cases, consider sucralfate and/or Gaviscon as supportive care to be taken at least 2hr after ingestion of the last capsule of GSK2141795, so as to avoid any potential drug-drug interactions.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Permitted Medications

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of screening until the end of the clinical phase of the study. Any concomitant medications, including over-the counter medications, herbal preparations and alternative therapies, taken during the study will be recorded in the CRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, erythopoeitin and G-CSF support, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Subjects should not receive those medications listed as prohibited in Section 5.2.2.

5.2.2 Prohibited Medications

Subjects should not receive other anti-cancer therapy or other investigational drug while on study treatment, except for megestrol [Megace] if used as an appetite stimulant is allowed.

Patients should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to the first dose of either study drug until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. The investigator should contact a CTEP Medical Monitor before initiating treatment with any herbal preparation.

The following medications (including but not limited to) are prohibited during the study:

PROHIBITED – highly sensitive and/or low therapeutic index CYP3A/CYP2C8/BCRP/CYP3A4 substrates since concentrations of these drugs may be increased	
CYP3A Substrate	**Therapeutic Area**
Cisapride	Hypnotics and Sedatives
Pimozide	Antidepressant, Antipsychotics, Antianxiety agents
Astemizole	Antihistamine
BCRP Substrate	**Therapeutic Area**
Rosuvastatin,sulfasalazine	HMG-CoA Reductase Inhibitors, gastrointestinal agents
PROHIBITED – strong inducers/inhibitors of CYP3A4	
Strong CYP3A4 Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (*e.g.*, rifampin, rifabutin, rifapentine), troleandomycin	Antibiotics
Itraconazole, ketoconazole	Antifungals
Nefazodone	Antidepressants
atazanzvir, delaviridine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, nevirapine	Antivirals
carbamazepine, phenobarbital, phenytoin	Anticonvulsants

5.2.3 Cautionary Medications:

The following medications (including but not limited to) that may alter the concentrations of trametinib or GSK2141795 or have their elimination altered by trametinib or GSK2141795 should be administered WITH CAUTION:

USE WITH CAUTION – Drugs Potentially Affecting trametinib or GSK2141795 concentrations	
Drug	**Therapeutic Area**
quinidine, diltiazem, verapamil	Antiarrhythmics:
fluvoxamine, fluoxetine, paroxetine,nefazodone	Antidepressants:
aprepitant, cimetidine	Antiemetics
fluconazole, terbinafine, voriconazole	Antifungals
ciprofloxacin, erythromycin, isoniazid	Anti-infectives
Mibefradil, diltiazem, verapamil	Calcium Channel Blockers
aprepitant, oxandrolone, tizanidine, gemfibrozil	Miscellaneous
USE WITH CAUTION – Drugs that may inhibit P-gp and BCRP	
Drug	**Therapeutic Area**
Valspoda	Miscellaneous
Atorvastatin	HMG-CoA Reductase Inhibitors
Carvedilol	Congestive Heart Failure
Methadone	Analgesic
Meperidine	Narcotic
Omeprazole	Proton Pump Inhibitor
USE WITH CAUTION – Drugs that may have their concentrations altered by trametinib or	

GSK2141795	
Drug	**Therapeutic Area**
Repaglinide, rosiglitazone, pioglitazone	Antidiabetics
alfentanil, fentanyl	Analgesics
Quinidine	Antiarrhythmics
Cilostazole	Anticoagulants and Antiplatelets
Astemizole	Antihistamines
diergotamine, ergotamine, eletriptan	Antimigraine agents
Pimozide	Antipsychotics
Buspirone	Anxiolytics
Felodipine	Calcium Channel Blockers
sildenafil, tadalafil, vardenafil	Erectile Dysfunction agents
cerivastatin,ovastatin, simvastatin, atorvastatin	HMG-CoA Reductase Inhibitors
Alprazolam, diazepam, midazolam, triazolam	Hypnotics and Sedatives
cyclosporine, sirolimus, tacrolimus	Immunosuppressive agents
Cisapride	Prokinetic agents
cyclosporine, torsemide, chloroquine, zopiclone	Miscellaneous
Eperenone	Selective Aldosterone Blockers
chloroquine, zopiclone	Thiazolidinediones

Use of repaglinide, rosiglitazone, and/or pioglitazone is permitted only after consultation with the CTEP Medical Monitor.

Oral steroids should be used with caution and subjects monitored for steroid-induced hyperglycemia. Short courses (up to a maximum of 14 days) of oral corticosteroids intended to treat study treatment related rash or diarrhea are allowed. Budenoside is recommended for supportive care of diarrhea.

Subjects will be instructed to inform the investigator before taking any of these or any other medications. Investigators (or their appropriate designee) will be expected to review concomitant medications with the subject at each clinical visit. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Appendix C is a patient information sheet that can be used for this specific protocol and presented to the patient.

5.2.4 Prophylaxis medications

The following medications are recommended as prophylaxis during the first 4 cycles of treatment due to an increased incidence of Shingles and infection noted on patients in this trial:

- Shingles prophylaxis: Valtrex 500mg OD is preferred otherwise acyclovir 400mg bid can be used

- Infection prophylaxis: Ciprofloxacin or Moxifloxacin

The prophylaxis recommendations above are an additional care measure while determination as to whether there is reasonable possibility, that Trametinib and GSK2141795 caused the increased incidence of shingles or infection (urinary tract or upper respiratory) noted in the patients on this trial.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Clinical progression,
- Patient non-compliance
- Pregnancy
  - All women of child bearing potential (WOCBP) should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor.

5.4 Duration of Follow Up

Patients will be followed for 4 weeks after removal from study treatment or until death, whichever occurs first. Adverse event(s) related to study treatment will be followed until resolution to a $\leq$ grade 1 or until the adverse event remains stable at the same grade for at least 2 months.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Trametinib and/or GSK2141795 Dose Modifications

The table below outlines the dose levels to be used for any necessary trametinib dose modifications when dosing trametinib as a single agent:

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD
-2	1 mg QD

If GSK2141795 is added for disease progression after 2 cycles or because of failure to achieve a PR after 4 cycles then the dose of tramentinib will be reduced to 1.5 mg and combined with 50 mg pf GSK2141795 administered daily.

The table below outlines the dose levels to be used for any necessary trametinib dose modifications when trametinib is dosed with GSK2141795:

Dose Level	Trametinib Dose/Schedule
0	1.5 mg QD
-1	1.0 mg QD
-2	0.5 mg QD

The table below outlines the dose levels to be used for any necessary GSK2141795 dose modifications:

Dose Level	GSK2141795 Dose/Schedule
0	50 mg QD
-1	25 mg QD

A maximum of two Trametinib and/or one GSK2141795 dose level reductions are allowed. Patients may have up to 2 dose level reductions of Trametinib while taking Trametinib alone (lowest dose allowed is 1 mg QD). Patients may have a further 2 dose level reductions of Trametinib while taking Trametinib in combination with GSK2141795 (lowest dose allowed is 0.5 mg QD).

6.1.1 Trametinib or GSK2141795 Dose Modification for Toxicities Hematological/ Non-Hematological Toxicities Not Otherwise Specified in Subsequent Sections

The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment and make the appropriate change for that drug.

Study Drug(s) Modification for Clinically Significant Toxicities Deemed Related to Study Drug(s) (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, visual changes, neutropenia, or thrombocytopenia. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards	Continue trametinib and/or GSK2141795 at current dose level.
Grade 2		• Interrupt trametinib and/or GSK2141795 until resolution to grade 1 or baseline. • Upon resolution, restart trametinib and/or GSK2141795 at current dose level.
Grade 3		• Interrupt trametinib and/or GSK2141795 until resolution to grade 1 or baseline. • Upon resolution to baseline or grade 1, restart the interrupted agent(s) with one level of dose reduction • If the Grade 3 toxicity recurs, interrupt trametinib and/or GSK2141795; When toxicity resolves to Grade 1 or baseline, restart the interrupted agent(s) **reduced by another dose level**
Grade 4		Permanently discontinue trametinib and/or GSK2141795.
Study drug(s) should be discontinued if treatment delay is ≥28 days due to toxicities. If the investigator concludes that continued study drug(s) will benefit a patient, the study chair and CTEP Medical Monitor may be consulted for the possibility of resuming study drug(s), provided that toxicities have resolved to baseline or grade 1.		

6.1.2 Trametinib and/or GSK2141795 Dose Modification for Rash

Rash is a frequent AE observed in patients receiving trametinib (Investigator's Brochure, 2012a) or GSK2141795. Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula *et al.*, 2010; Lacouture *et al.*, 2011).

Further, two types of rashes may be seen with the trametinib + GSK2141795 combination:

- Acneiform rash, typically associated with tramentinib.
- Maculopapular rash, often associated with pruritus GSK2141795.

If the diagnosis is unclear, a biopsy and photographs should be obtained as well as a dermatology consult.

In general, topical and oral antibiotics play a larger role in management of the trametinib acneiform rash, while topical and oral steroids are more relevant to the management of the GSK2141795 maculopapular rash. Subjects should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to subjects who experience a rash while on study. The following information is a guideline.

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair or the CTEP Medical Monitor may be required.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/ Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily, starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (*e.g.*, clindamycin) or oral antibiotics (*e.g.*, doxycycline 100 mg BID, minocycline 100 mg BID).
Symptomatic Care[b]	Upon the first signs of rash, mild strength topical steroid (e.g. hydrocortisone 1% cream) with escalation to higher strength and/or oral steroid as detailed below. • Upon the first signs of papulopustular (acneiform) rash consider doxycycline (100 mg BID) or minocycline (100 mg BID). • Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath and local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics. • For subjects who had study drug reduced because of rash, re-escalation may be considered if toxicity does not recur with a re-challenge at a lower dose.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Study Drug(s) Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib and/or GSK2141795. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib and/or GSK2141795 by one dose level**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib and/or GSK2141795 by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ grade 1. • **Restart trametinib and/or GSK2141795 at reduced dose level.**[3]
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • For papulopustular (acneiform) rash consider doxycycline 100 mg bid or minocycline 100 mg bid. • Consult dermatologist.	• Interrupt trametinib and/or GSK2141795 until rash recovers to ≤ grade 1. • **Restart with trametinib and/or GSK2141795 reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 28 days, **permanently discontinue trametinib and/or GSK2141795**.
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone priopionate 0.5% cream. 3. Approval of CTEP Medical Monitor is required to restart study treatment after ≥28 days of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

6.1.3 Trametinib Dose Modifications for Visual Changes

Trametinib is known to be associated with visual adverse events. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (*e.g.*, retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (*i.e.*, branch or central retinal vein occlusions [RVO]).
The ophthalmology exam will include best corrected visual acuity, visual field examination, tonometry, direct fundoscopy, and indirect fundoscopy. Optical coherence tomography is recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including visual field examination, fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the tables below.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose level. • If RPED suspected/diagnosed: See RPED dose modification table below (following this table); **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the CTEP Medical Monitor. • **If RVO or RPED, permanently discontinue trametinib**.
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

Trametinib Dose Modification for RPED	
Event CTCAE Grade	**Action and Dose Modification**
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

6.1.4 Trametinib and/or GSK2141795 Dose Modification for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib or GSK2141795 (Investigator's Brochure, 2012a). Other frequent causes of diarrhea may include concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded.

Guidelines regarding management and dose modification for diarrhea considered related to trametinib and/or GSK2141795 are provided in the table below.

Management and Study Drug(s) Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (bananas, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hous: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics.	• Continue study drug(s). • If diarrhea is grade 2 for > 48 h, interrupt study drug(s) until diarrhea resolves to grade ≤1. • Restart study drug(s) at the same dose level • If treatment delay is ≥28 days, discontinue study drug(s).

Management and Study Drug(s) Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt study drug(s) until diarrhea resolves to ≤ grade 1. • Restart with study drug(s) reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study drug(s)**. • If treatment delay is ≥28 days, discontinue study drug(s).
1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.1.5 Trametinib and/or GSK2141795 Dose Modification for Liver Chemistry Changes

Study Drug(s) Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
• ALT ≥3x ULN **but** <5x ULN **and** TB <2x ULN, **without** symptoms considered related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• **May continue study drug**. • Report as SAE if CTEP-AERS reporting criteria is met. • If **liver chemistry stopping criteria** are met any time, proceed as described below. **MONITORING:** Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT <3x ULN and TB <2 ULN).
Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib 1) ALT ≥3x ULN **and** bilirubin ≥2x ULN or >35% direct bilirubin [1, 2] 2) ALT ≥ 3x ULN **and** INR >1.5, if INR measured[2] (INR threshold does not apply if subject is on anticoagulant) 3) ALT ≥5x ULN 4) ALT ≥3x ULN persists for ≥4 weeks 5) ALT ≥3x ULN **and** cannot be monitored weekly for 4 weeks 6) ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	**Immediately discontinue study treatment.** • Do not restart/rechallenge unless approved by CTEP trametinib medical monitor. *[* • Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. • Perform liver event ASSESSMENT AND WORKUP (see below). • Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see MONITORING below). **MONITORING:** *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* • Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event follow-up assessments within 24 hours. • Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. • A specialist or hepatology consultation is recommended. *In patients stopping for criteria 2-6:* • Repeat LFT and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. **ASSESSMENT and WORKUP:** • Viral hepatitis serology.[4] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*:

Study Drug(s) Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[5] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN **and** INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants. 3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia) 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al*., 2005).	

6.1.6 Trametinib Dose Modification for Pneumonitis

Pneumonitis has been observed in patients receiving trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

Management and Study Drug Modification Guidelines for Pneumonitis		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection. • Monitoring of oxygenation via pulse-oximetry recommended. • Consultation with pulmonologist recommended.	Continue trametinib at current dose.
Grade 2	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests: If < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL recommended. • Symptomatic therapy including corticosteroids if clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is ≥ 28 days, **permanently discontinue trametinib**.
Grade 3	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is ≥ 28 days, **permanently discontinue trametinib**.
Grade 4	Same as grade 3.	**Permanently discontinue trametinib.**
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

6.1.7 Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHOs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks.[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Consult with the CTEP trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level.[b] – Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – **Permanently discontinue trametinib**. – Report as SAE – Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution. – Consult with the CTEP trametinib medical monitor.[c]
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib**. • **Report as SAE**. • **Consult with cardiologist**. • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.

[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
[b] Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the CTEP trametinib medical monitor is required.
[c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

6.1.8 Trametinib and/or GSK2141795 Dose Modification for QTc Prolongation

Study Drug(s) Withholding and Stopping Criteria for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level.[b] • **If the event does not resolve or recurs after restarting, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using Bazett's formula [a] Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. [b] if the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and the CTEP trametinib medical monitor agree that the subject will benefit from further treatment.	

6.1.9 Trametinib Dose Modification for Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff has been selected.
- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in three consecutive visits with blood pressure assessments from two readings as described above. Visits to monitor increased blood pressure can be scheduled independtly from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from Medical Monitor is required.		

6.1.10 GSK2141795 Dose Modification for Hypo- and Hyperglycemia

To reduce the risk of hyperglycemia, patients with abnormal fasting glucose values at screening will be excluded. In addition, patients with Type 1 diabetes will also be excluded; however, patients with Type 2 diabetes will be allowed if diagnosed ≥6 months prior to enrollment, and if presenting with regular hemoglobin A1C (HbA1C) ≤8% at screening. Patients will have glucose and insulin monitored during the study. If hyperglycemia is observed, supportive therapy will be provided according to standard medical practice. Treatment will be dose reduced or discontinued for clinically significant toxicity that cannot be adequately managed medically.

- (Mild) Fasting blood glucose > 150mg/dL (8.3 mmol/l)
  Monitor fasting and preprandial glucose.

- (ModeratetoSevere) Fasting blood glucose <70 mg/dL (3.9 mmol/l) OR any blood glucose >250 mg/dl (13.9 mmol/l)
  Instruct subject to hold study drug(s) and notify investigator immediately. The investigator should discuss intervention and possible resumption of GSK2141795 with the study chair and CTEP sponsor

If a blood glucose > 250 mg/dL (13.9 mmol/l) is observed the subject should be monitored for ketoacidosis as clinically indicated. If subject has evidence of ketoacidosis, then treatment should be undertaken with awareness that the action of insulin or other antihyperglycemic agents (e.g. sulfonylureas, biguanides, etc.) may be substantially blocked by the action of the GSK2141795. The action of insulin or other antihyperglycemic agents should be restored as GSK2141795 is cleared. If an antihyperglycemic agent is administered, then the subject should be observed closely for rebound hypoglycemia as GSK2141795 is cleared. Intravenous insulin treatment is recommended.

6.1.11 GSK2141795 Dose Modification for Mucositis

Mucositis has been observed as a dose-limiting toxicity of GSK2141795
.

Event Name	**Mucositis**	
Grade of Event	**Management**	**Dose Modification**
Grade 1-2	Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.	No change in dose Hold until ≤ Grade 1. Resume at same dose level.
Grade 3-4	Above, plus systemic opiate administration as needed. Consider IV hydration and hospital admission as appropriate. Temporarily discontinue study drug(s) and discuss with GSK Medical Monitor.	Temporarily discontinue GSK2141795 and discuss with study monitor. Hold* until < Grade 2. Resume at one dose level lower.
*Patients requiring a delay of ≥ 28 days should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

6.1.12 Trametinib and/or GSK2141795 Dose Modification for Neutropenia

Event Name	Neutropenia	
Grade of Event	**Management**	**Dose Modification**
Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3-4	Hold only for febrile neutropenia (single temperature of > 38.3C OR a sustained temperature of ≥ 38C for more then 1 hour) OR grade 4 neutropenia (ANC < 500/ul)	Hold until < Grade 2. GCSF therapy may be started at the discretion of the treating physician. The dose of study drug(s) may be maintained if neutropenia was the only study drug related toxicity requiring dose modification and GCSF treatments are continued. Otherwise decrease by one dose level.
*Patients requiring a delay of ≥ 28 days should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

6.1.13 Trametinib and/or GSK2141795 Dose Modification for Thrombocytopenia

Event Name	Thrombocytopenia	
Grade of Event	**Management**	**Dose Modification**
Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3-4	Hold only for grade 3 (< 50,000/ul) with bleeding ≥grade 2 OR grade 4 thrombocytopenia (< 25,000/ul)	Hold* until platelet count has recovered to 30,000/ul. For grade 4 thrombocytopenia resume at one dose level lower, if indicated.
*Patients requiring a delay of ≥ 28 days should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the

Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required. *Frequency is provided based on 968 patients.* Below is the CAEPR for Trametinib dimethyl sulfoxide (GSK1120212B).

Version 2.3, October 26, 2015[1]

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 968]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 968]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
INFECTIONS AND INFESTATIONS			
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Periorbital edema		

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 968]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pruritus		***Pruritus (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (folliculitis)		***Skin and subcutaneous tissue disorders - Other (folliculitis) (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[4]			***Skin and subcutaneous tissue disorders – Other (rash)[4] (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 2)***
Vascular disorders - Other (edema)[5]			***Vascular disorders - Other (edema)[5] (Gr 2)***
	Vascular disorders - Other (hemorrhage)[6]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Visual disorders include visual disturbance that can be associated with retinal hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, intraocular pressure increased, macular edema, visual acuity reduced, and vitreous detachment.

[3]Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[4]Skin and subcutaneous tissue disorders - Other (rash) may include rash, rash acneiform, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, and skin fissures.

[5]Edema includes edema, lymphedema, and edema limbs.

[6]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on Trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy
EYE DISORDERS - Eye disorders - Other (corneal graft rejection); Eye disorders - Other (cyclitis); Eye disorders - Other (eye nevus); Eye disorders - Other (intraocular pressure

increased); Eye disorders - Other (iritis); Eye disorders - Other (vitreous detachment); Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Papilledema; Photophobia
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Enterocolitis; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (obstruction gastric); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu-like symptoms; General disorders and administration site conditions - Other (axillary pain); General disorders and administration site conditions - Other (pneumatosis); Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain
INFECTIONS AND INFESTATIONS - Biliary tract infection; Device related infection; Enterocolitis infectious; Infections and infestations - Other (abscess limb); Pharyngitis; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Platelet count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Metabolism and nutrition disorders - Other (hyperphosphatemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (compression fracture); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (dysuria); Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hot flashes; Hypotension; Thromboembolic event (venous)

Note: Trametinib dimethyl sulfoxide (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for GSK2141795 (NSC 767034)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 150 patients. Below is the CAEPR for GSK2141795.

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, July 26, 2013[1]

Adverse Events with Possible Relationship to GSK2141795 (CTCAE 4.0 Term) [n= 150]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Esophagitis		
	Gastrointestinal mucositis[2]		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypoglycemia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Respiratory mucositis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal mucositis may include Anal mucositis, Mucositis oral, Rectal mucositis, or Small intestinal mucositis under the GASTROINTESTINAL DISORDERS SOC.

[3]Respiratory mucositis may include Laryngeal mucositis, Pharyngeal mucositis, or Tracheal mucositis under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC

Also reported on GSK2141795 trials but with the relationship to GSK2141795 still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Cardiac arrest, Left ventricular systolic dysfunction, Ventricular tachycardia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Wound infection
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Ejection fraction decreased; GGT increased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hyponatremia, Hypophosphatemia
NERVOUS SYSTEM DISORDERS - Dysgeusia; Dysphasia
RENAL AND URINARY DISORDERS - Acute kidney injury
VASCULAR DISORDERS - Thromboembolic event

Note: GSK2141795 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. Each site will submit the electronic version of the CTEP-AERS report to the PMH Phase II Consortium Central Office. Once review by the lead group coordinator has taken place the report will be forwarded to NCI. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

In order to ensure the timely fulfillment of both US and Canadian IND regulatory reporting requirements, all CTEP-AERS reports must be sent to the PMH Phase II Consortium Central Office within 3 working days from the date the event was known to the investigator.

- In the unlikely event that an adverse event occurs that does not meet the reporting requirements for CTEP-AERS, but does meet the definition of a Serious Adverse Event, an CTEP-AERS report must still be completed and sent to the Central Office within 3 working days of the event being known to the investigator. The event must be telephoned or e-mailed to Central Office within 1 working day.

- The PMH Phase II Consortium Central Office will be responsible for reporting to Canadian regulatory authorities all Serious Adverse Events that are both unexpected and related to study drug. The Central Office will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the Central Office by the NCI U.S.

Investigators must notify their local Research Ethics Boards (REB/IRBs), according to their guidelines, of all SAE reports from their centre and file the report in their regulatory study binder. In addition, all reports sent out to centres by the PMH Phase II Consortium Central Office must be sent to local REB/IRBs, according to their guidelines. Documentation from the REB/IRB of receipt of these reportable events must be kept on file in each institution's regulatory binder.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

○ "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.
[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:** • All Grade 4, and Grade 5 AEs **Expedited 10 calendar day reports for:** • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events [2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period. Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

7.3.4.1 For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (i.e. Adverse Events Form in the eCRF, see Section 7.4):

CTCAE SOC	Adverse Event	Grade
Blood and lymphatic system disorders	Anemia	Grade 3
Investigations	White blood cell decreased	Grade 3
	Lymphocyte count decreased	Grade 3 or 4
	Neutrophil count decreased	Grade 3
	Platelet count decreased	Grade 3
Skin and subcutaneous tissue disorders	Rash pustular	Grade 3
	Rash acneiform	Grade 3

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary

malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

8.1 CTEP IND Agent(s)

8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Chemical Name (IUPAC): equimolecular combination acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro6,8-dimethyl- 2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl] with 1,1'-sulfinylbis[methane]

Other Names: trametinib, GSK1120212, JTP-74057, JTP-78296, JTP-75303, Mekinist

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ **M.W.:** 693.54

Approximate Solubility: Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)

Mode of Action: Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

Description: Trametinib dimethyl sulfoxide is a white to almost white powder.

How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets.

Investigationally labeled bottles each contain 32 tablets packaged in high density polyethylene bottles with child-resistant closures including an induction seal liner.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of Opadry Yellow 03B120006 (hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow).

- 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of Opadry Pink YS-1-14762-A (hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red).

Each commercially-labeled bottle contains 30 tablets with a desiccant.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated with 'GS' debossed on one face and 'TFC' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.

- 2 mg tablets are pink, round, biconvex and film-coated with 'GS' debossed on one face and 'HMJ' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

Storage: Store tablets at 2°C -8°C in the original bottle. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12

hours until the next scheduled dose.

Potential Drug Interactions: : *In vitro* studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c and CES2). M5 is eliminated by CYP3A4 and other pathways, presenting the clinically relevant, albeit low, potential for drug-drug interaction. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8, and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 MRP2 and MATE1.
.

Availability: Trametinib dimethyl sulfoxide (GSK1120212B) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Trametinib dimethyl sulfoxide (GSK1120212B) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 GSK2141795 (NSC#)

Chemical Name: N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

Other Names: GSK2141795C

Classification: pan-AKT inhibitor

CAS Registry Number: 1047634-65-0

Molecular Formula: $C_{18}H_{16}Cl_2F_2N_4O_2$ **M.W.:** 429.25 g/mol

Approximate Solubility: Very slightly soluble in water at room temperature (0.18 mg/mL). Solubility decreases as pH increases; for example solubility in gastric fluid at 37° C is >11 mg/mL.

Description: white to off-white powder

How Supplied: GSK2141795 capsules are supplied by GlaxoSmithKline and distributed by the DCTD, NCI. The 25 mg capsule is a size 2 Swedish orange opaque body and Swedish orange opaque cap with no markings. The capsule contains active pharmaceutical ingredient, microcrystalline cellulose, and magnesium stearate. The capsules are packaged in white high density polyethylene (HDPE) bottles with white plastic, induction-seal, child-resistant caps. Each

bottle contains 35 capsules.

GSK does not have stability data to support repackaging GSK2141795 capsules. Capsules must be dispensed in the original container.

Storage: Store bottles at 2-8° C (36-46° F).

Stability: Shelf life studies of GSK2141795 are on-going.

Route of Administration: Oral administration. Capsules must be taken fasting 1 hour following a meal and 2 hours before the next meal. The following guidelines are recommended:
Eat a small snack followed by 60 minutes of fasting prior to taking GSK2141795. Water is allowed during this fasting period. If possible, take each GSK2141795 capsule approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz). Remain upright for 30 minutes after taking the last capsule of GSK2141795.
Fast for 2 hours after ingestion of the last capsule of GSK2141795. Water is allowed during this fasting period.
Potential Drug Interactions: *In vitro* data suggest GSK2141795 is a substrate of CYP450 3A4. Potent inhibitors and inducers of 3A4 are prohibited. GSK2141795 appears to be a moderate inhibitor of CYP 2C8 and 3A4 by *in vitro* testing. Drugs that are substrates of these isoenzymes should be used with caution and ones with a narrow therapeutic index should be avoided.

GSK2141795 is a substrate of p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). It is also an inhibitor of BCRP and OATP1B1. Administration of sensitive BCRP substrates should be prohibited, such as topotecan.

Availability

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-

ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

As a companion study to the proposed clinical trial, we will conduct studies aimed at identifying predictors of response and pharmacodynamic (PD) studies to demonstrate target inhibition and to define mechanisms of action and resistance. For the purposes of the current trial, we will obtain a research peripheral blood sample* and BM aspirates at the following time points:

1) study screening +/- cycle 1/day 1 pre-dosing*
2) cycle 2/Day -2 to 1, 2-4 hours following administration of trametinib
3) progression on single agent trametinib**
4) cycle 2 (trametinib+GSK2141795)/Day -2 to 1, 2-4 hours following administration of trametinib in combination with GSK2141795
5) at progression on trametinib + GSK2141795**

For biomarker positive patients only blood samples will only be collected at each BM sampling time point at every even cycle. All patients however require a peripheral blood sample at screening.
*cycle 1/day 1 BM will only be done if insufficient material is obtained at screening for the proposed correlative studies
**to be performed only if the patient has responded (PR or better) and then progressed

9.1.1 Sample Procurement

Sample procurement and shipping instructions are provided in the Protocol Lab Manual.

Approximately 6-15 mls of bone marrow (2-5 mls from each from 3 separate pulls) will be procured for the purposes of correlative studies. Samples from all participating centers will be shipped overnight to PM Cancer Centre.. All samples will be sent directly to PM Cancer Centre by overnight shipment.

The lab samples will be processed upon arrival. From the first tube, mononuclear cells (MNCs)

from will be prepared by Ficoll-Hypaque gradient and myeloma cells will be purified by immunoselection with anti-CD138-conjugated immunomagnetic beads. Experience indicates that approximately 4 million CD138 selected myeloma cells can be obtained from 2 mls of whole BM. One million cells will be aliquoted for DNA extraction and 1 million cells aliquoted for RNA extraction. Any remaining material will be employed to generate cytospin slides for tissue arrays and/or frozen in DMSO as viable cells and stored in liquid nitrogen. These will be banked for future validation and exploratory studies. The second green-top tube will be reserved for flow cytometry studies as described below. The third tube will be reserved for reverse phase protein assays (RPPA) as discussed below.

9.1.2 Next Generation Sequencing

Our hypothesis is that patients whose tumors harbor mutations of KRAS, NRAS or RAF (reported in 21%, 19% and 7% of MM cases, respectively) will preferentially respond to MEK inhibition. To test this hypothesis and, to potentially enhance the effect size, we have chosen to stratify patients based on the presence or absence of mutations of RAS or RAF. For the purpose of patient stratification, mutational analysis will be performed by the University Health Network CLIA certified molecular diagnostic lab using the sequenom platform. This biomarker study is considered integral to the trial.

Genomic DNA (450 ng) extracted from purified CD138 positive myeloma cells will be submitted to the clinical lab for next generation sequencing that allows for a comprehensive screen of mutations including those of NRAS, KRAS and BRAF (see Appendix F Table 1 and 2 for the complete list of genes and mutations for the TruSeq Amplicon Cancer Panel and TruSight Tumor Panel. Cases that are positive for mutations of RAS or RAF will be stratified to the biomarker positive groups (see Appendix F, Table 3 for the list of RAS and RAF mutations that define the biomarker positive group). The lower limit of detection of these next generation sequencing panels is 5-10%. This means mutations present at levels below 10% may be missed.

The mutational profile will be provided to the site investigator and the report kept in the study chart. The information should be disclosed to the treating physician and patient and included in the clinical note. The Principal Investigator will be responsible for assignment of patients to the biomarker positive or negative groups. Each group will enroll 12 patients in the first stage. If the pre-determined response criteria are met during the first stage in either or both groups then an additional 25 patients will be enrolled in either or both groups in the second stage.

9.1.3 MAF expression

In MM tumors that harbor the t(4;14) translocation or translocations that dysregulate MAF transcription factors (30% of MM cases) the MEK-ERK pathway appears to upregulate expression of MAF and inhibition of MEK selectively induces apoptosis of MAF-expressing myeloma tumors (Annunziata *et al.,* 2011). These pre-clinical studies suggest that this subgroup of myeloma patients may preferentially respond to MEK inhibitors. To test this hypothesis RNA derived from screening BM samples will be used to quantify MAF expression (*c-maf, MAF-B and MAF-A*) by quantitative RT-PCR (qPCR) as described in the lab manual (Mao *et al.*, 2007). As shown in the figure 1, there is 100% correlation between cMAF and MAFB expression and

FISH translocation and protein expression by Western blot. As this assay has not yet been validated, the specificity and sensitivity of this assay is to be determined. As such, this assay will not be used to stratify patients; however, response rates will be correlated with MAF expression as an exploratory endpoint. RNA from the first 12 patients enrolled in each stratification group (see above) will be batched and evaluated in an interim analysis for correlation with efficacy. If the data indicate that MAF may be a predictive biomarker the protocol may be modified to enrich for this subgroup of patients.

In additon to determining the correlation with response to trametinib, the relationship between MAF expression and chromosomal abnormalities will be detected by qPCR and FISH, respectively (figure 1). FISH is a standard molecular assay performed in cases of multiple myeloma. Evidence suggests that high levels of MAF occur in myeloma tumors with translocations t(14:16) that dysregulates cMAF, t(14:20) that dyregulates MAFB, as well as t(4;14) that results in overexpression of FGFR3 and MMSET (Annunziata *et al*., 2011). As an exploratory endpoint therefore we will determine the correlation between these two molecular assays (qPCR and FISH). We propose that this will provide information for better clinical interpretation of an assay that is already employed as standard of care for multiple myeloma.

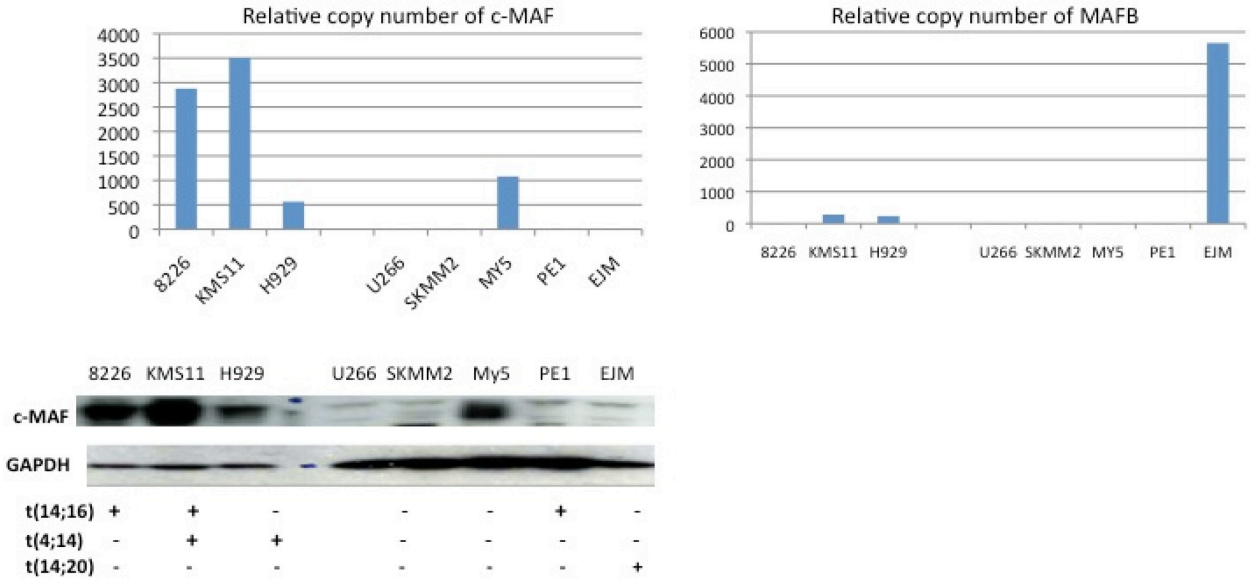

Figure 1. MAF expression by qPCR and Western blot analysis. The graph on the right demonstrates expression c-MAF by qPCR relative to the housekeeping gene h36B4 and SKMM2 cells as a negative control. Copy numbers correlate 100% with protein expression determined by Western blot (shown below) and t(14:16) and t(4;14) translocation. The graph on the left demonstrates expression of MAFB by qPCR. Expression of MAFB correlates with the t(14;20) translocation. Not shown is data for MAFA as no cell exist with translocations that dysregulate MAFA.

9.1.4 Expression of integrin-β7

Integrin-β7 is a cell surface protein whose expression is regulated by MAF transcription factors (Hurt *et al.,* 2004). We hypothesize therefore that integrin-β7 may serve as a surrogate marker

for MAF-expressing myeloma tumors which as described above, represent a subgroup of myeloma tumors with increased sensitivity to MEK inhibitors. As cell surface expression can readily be detected by flow cytometry, integrin-β7 has the potential to serve as a predictive biomarker that can easily translate to the clinical lab. As an exploratory endpoint we will measure integrin-β7 on CD138 positive myeloma cells and correlate positivity with qPCR expression of MAF genes and clinical responses. An aliquot of whole BM obtained at screening will be labeled with anti-CD138-FITC and anti-integrin-β7-PE or isotype control. Flow cytometry will be done using a LSR II flow cytometer (BDIS), and offline listmode analysis will done using FlowJo software. Details of the methodology are provided in the lab manual. The sensitivity and specificity of the assay is yet to be determined.

9.2 Pharmacodynamic (PD) Studies

9.2.1 Flow Cytometry PD Studies

Myeloma cells from BM samples will be evaluated for target modulation and the effects of trametinib with or without GSK2141795 on downstream signaling targets of RAS-MEK-ERK signaling and alternative pathways (PI3K/AKT). Flow cytometry is a highly developed technique for the diagnosis of hematological malignancies, based on the correlated measurements of multiple surface immunophenotypic markers plus forward and orthogonal light scattering characteristics of cell subpopulations. However, the recent introduction of techniques that measure the activation states of signaling pathways using phosphospecific antibodies, the scope of flow cytometry now extends into molecular therapeutic monitoring in the clinic (Tong *et al.,* 2006). By using flow cytometry applications, we will determine whether the MEK target ERK, is activated in myeloma cells pre-treatment and whether administration of trametinib inhibits ERK phosphorylation in primary cells. Further, we will determine whether at progression, ERK phosphorylation remains suppressed despite trametinib treatment providing valuable insights into whether escape mechanisms are ERK-independent (ERK remains inactive) or ERK-dependent (ERK is phosphorylated). In addition, will evaluate whether the PI3K/AKT pathway is activated at baseline, is induced in response to single agent trametinib or at progression, as a potential mechanisms of acquired resistance. The results will be correlated to response to trametinib +/- GSK2141795 and analyzed as an exploratory endpoint. We hypothesis that patient with constitutive ERK phosphorylation and lacking AKT activation will respond to trametinib alone; that patients who fail to respond or progress on trametinib alone will benefit from the addition of GSK2141795, if AKT is constitutively activated in the cells; and that patients who progress by ERK-dependent mechanisms may not benefit from the addition of GSK2141795.

We have experience at applying this technique for PD monitoring in early phase clinical trials (De *et. al.,* 2013). As shown in Figures 2 and 3, we have developed an assay that captures dynamic changes in intracellular levels of phosphoproteins in myeloma and CLL primary cells derived from patients on clinical trials of PI3K/AKT inhibitors. In a representative case (Figure 1) CD138 cells derived from a patient prior to dosing with SF1126 (PI3K inhibitor) demonstrate lack of constitutive AKT activity (ex vivo treatment with the PI3K inhibitor, LY294002 does not suppress AKT phosphorylation) however the pathway can be activated ex vivo by IGF-1. In this phase I study treatment with a subtherapeutic dose of SF1126 partially suppressed IGF-1 induced phosphorylation in CD138 cells derived post-dosing on days 1 of cycles 1 and 2. In the second

example, we observed modest constitutive activation of AKT and its downstream targets GSK3 and pS6 in CLL cells derived from a patient prior to dosing with the AKT inhibitor, GSK2141795. This is suggested by the decrease in phosphorylation of these proteins in response to ex vivo LY294002 treatment. This pathway can be further activated by stimulating with anti-IgM (BCR ligand) or by the addition of PMA. In contrast after 7 days of oral treatment with GSK2141795, basal and induced phosphorylation of downstream AKT targets (GSK3 and pS6) is completely suppressed in this same patient. On the other hand, RAS-MEK-ERK signaling is enhanced in post-treatment samples. Details of the flow cytometry protocol are provided in lab manual. The sensitivity of this assay is yet to be determined.

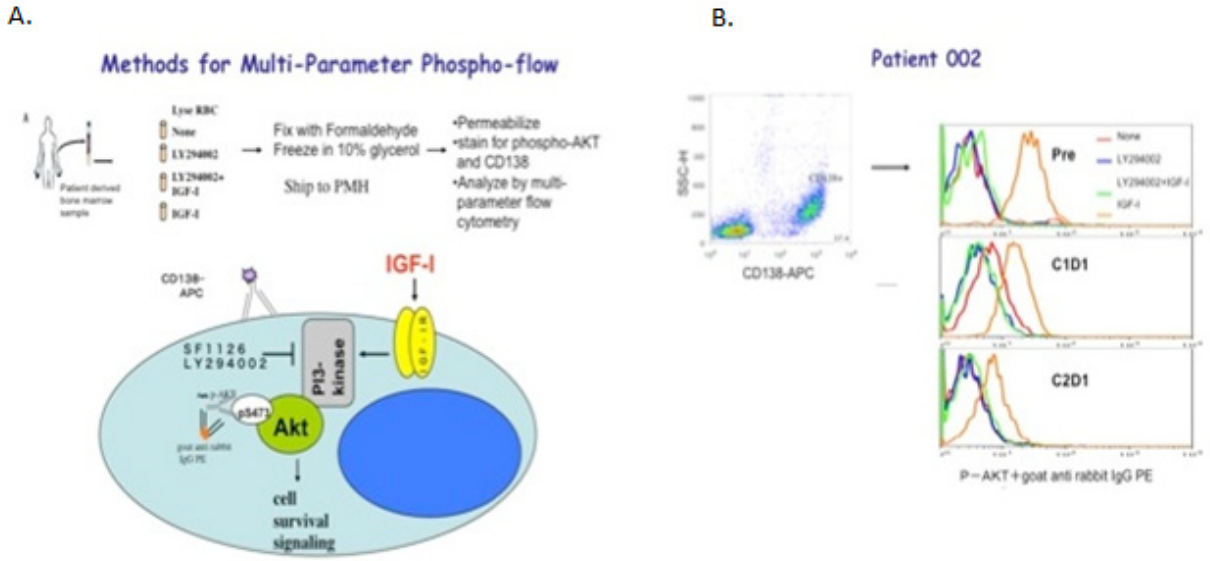

Figure 2a: Methodology for PD analysis on SF1126 Phase I clinical trial for MM. Figure 2b: phospho-AKT expression in CD138 gated myeloma cells. Pre-treatment (screening marrow), on cycle 1 day1 and cycle 2 day 1 4 h after dosing with SF1126. IGF-1 can induces AKT phosphorylation however the response is reduced after treatment with SF1126. LY294002 fails to inhibit AKT phosphorylation suggesting that AKT is not constitutively activated (De et al., 2013).

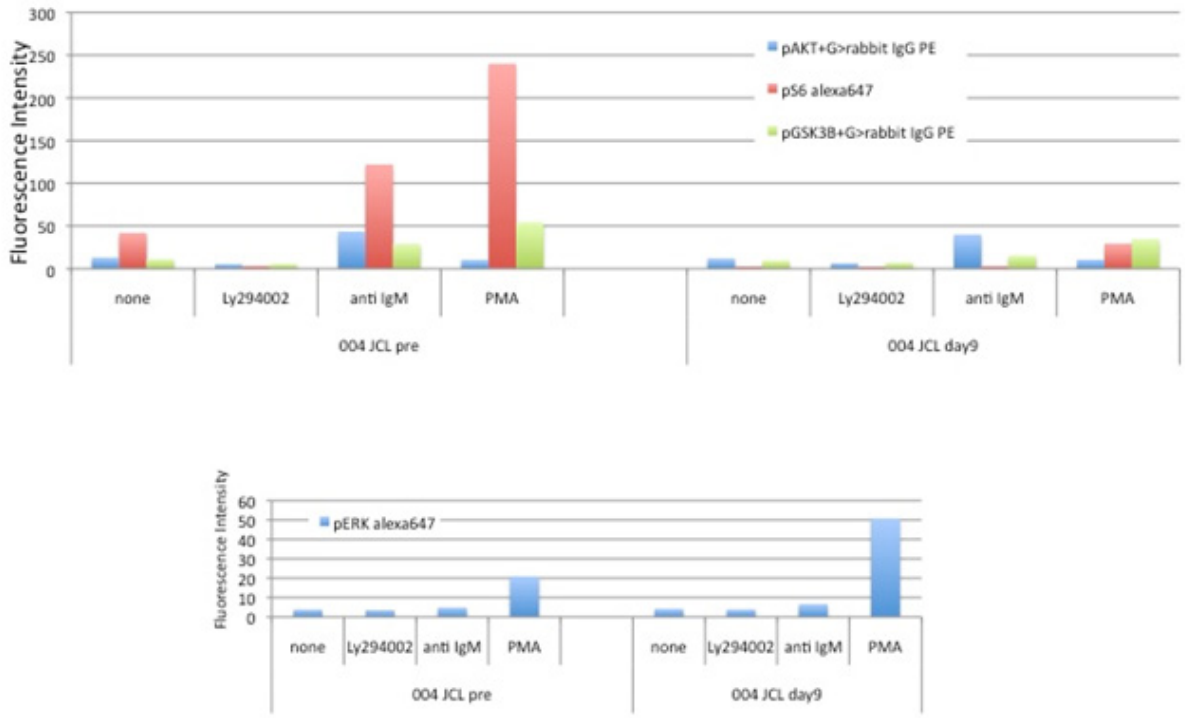

Figure 3: Mean fluorescence intensity (MFI) phospho-proteins in CD19 gated CLL cells. Pre-treatment (screening peripheral blood sample) on cycle 1 day 8 and after dosing with GSK2141795. Anti-IgM activates PI3K/AKT signaling as shown by increased AKT, GSK3 and pS6 phosphorylation however the response is completely blunted after GSK2141795 treatment for 7 days. RAS-MEK-ERK signaling however is enhanced after treatment.

9.2.2 Reversal Phase Protein Arrays (RPPA):

RPPA is a quantitative assay that analyzes nanolitre of sample for potentially hundreds of proteins (Iadevaia *et al.,* 2010). This antibody-based assay determines levels of protein expression, as well as protein modifications such as phosphorylation. RPPA allows concordant interrogation of multiple signaling molecules and their functional status. In essence, the RPPA study has major strengths in identification and validation of cellular targets, characterization of signaling pathways and networks, as well as determination of on and off target activity of drugs. We hypothesize that the integrated information derived from RPPA will display functional outcomes affected by MEK and/or AKT inhibition that will confirm target modulation and inform on predictors of response or mechanisms of resistance. As an exploratory endpoint each sample subjected to RPPA will be analyzed for effects on cell cycle, apoptosis, functional proteomics, and signaling network activity. The results across patients will be classified and compared with clinical responses to generate a "molecular signature" of functional outcomes affected by MEK and/or AKT inhibition.

In order to preserve the phospho-epitopes in samples that are shipped overnight and thus reduce the risk of false PD readouts, a BM pull will be immediately placed into a collection tube containing fix/lyse buffer. We have used this whole BM fixation and RBC lysis protocol for flow

cytometry applications (Chow *et al.,* 2008) and demonstrated that phospho-epitopes and CD surface markers are preserved and thus allows for CD138 selection of myeloma cells. The CD138 selected cells will then be snap frozen and serial samples batched for preparation of protein lysates using and shipping to the MD Anderson RPPA core facility. Their RPPA platform incorporates 130 validated antibodies that cover a wide spectrum of signaling molecules. A more detail description of sample preparation for RPPA is provided in the lab manual. The MD Anderson RPPA facility has extensively validated antibodies suitable for RPPA however the feasibility of the protein extraction for RPPA application is yet to be determined.

The products of these correlative studies are to validate and identify novel biomarkers related to MM responses and outcomes to MEK inhibitors that may then enter into development as clinical assays. In addition, we expect to begin testing hypotheses around novel biomarkers and mechanisms of resistance that may inform combination strategies and guide the development of innovative, personalized therapeutics for MM and cancers and general.

9.3 RAS and BRAF mutation detection using circulating free DNA (cfDNA)

As a pilot study within this protocol, the feasibility of deriving cfDNA from patients for detection of mutations of RAS and BRAF will be assessed. Currently, the detection of RAS and BRAF mutations is carried out in tumor tissue by next generation sequencing. This requires bone marrow aspiration for derivation of tumor tissue and CD138 purification of myeloma tumor cells for DNA extraction. Recent studies have validated the detection of KRAS and BRAF mutations from circulating free tumor DNA (cfDNA). cfDNA was detected in 100% of patients with metastatic colorectal cancer and showed 100% specificity and sensitivity for BRAFV600E mutation and 98% specificity and 92% sensitivity for KRAS mutations (*Thierry AR et al. 2014*). Thus, this represents a minimally invasive and cost-effective method for identification of patients that are most likely to benefit from targeted therapy.

For patients that are biomarker positive peripheral blood will be collected at all applicable time points and will be processed as per the Study Lab Manual. cfDNA will be extracted using the QIAamp DNA MINI Blood kit (Qiagen) according to the manufacturer's protocol. The DNA will be used to perform ultra-deep sequencing of KRAS, NRAS and BRAF using a two-step PCR-based approach, TAm-Seq followed by Illumina sequencing.

Our goals are first to determine our ability to derive cfDNA at multiple time points. To compare the sensitivity and specificity of RAS and RAF mutational analysis of peripheral blood cfDNA compared to detection using standard methods from tumor specimens. To determine whether mutational load over the treatment course can be evaluated from cfDNA. It is hoped that this will lead to the development of a less invasive and more efficient platform for the identification of MM patients that may benefit from targeted therapies.

9.4 Laboratory Correlative Studies

Please see lab manual for Correlative studies collection, shipping, and process instructions.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy, unless specified differently in the study calendar. Scans and x-rays, ECHO/MUGA, and Ophthalmology exam must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. If pre-study assessments were done within 3 days of treatment initiation, they do not need to be repeated for cycle 1 day 1. For subsequent cycles (2+), day 1 assessments can be completed up to 48 hrs prior to day 1. All day 15 assessments can be completed up to 48 hrs prior to day 15. Baseline myeloma disease assessment can be done ≤4 weeks prior to the start of therapy (see 11.2.1). Response assessment can be done up to ≤ 7 days prior to the start of the next cycle to allow for treatment decisions to be made with regards to the addition of GSK2141795 for stable disease or progression prior the initiation of the next cycle.

PROCEDURES	Screen	Cycle 1-2 Single Agent (cycle=28 days)		Cycles 3+ Single Agent	Cycle 1-2 Combination		Cycles 3+ Combination	Off Study	Safety Follow-up
	Pre-Study	Day1	Day15	At the start of every Cycle	Day1	Day 15	At the start of every cycle		4 weeks (+ 3 days) after last treatment
Trametinib		A----------A			A*----------A*				
GSK2141795					B----------B				
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------X						X	
Physical exam	X	X		X	X		X	X	
Vital signs	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	
Fasting serum chemistry[a]	X	X	X	X	X	X	X	X	
TSH	X				X		X[j]	X	
Serum viscosity[m]	X								
ECG[b]	X	X	X	X		X		X	
Echocardiogram or MUGA	X	Every 12 weeks (use same methodology for baseline and follow up).							
Ophthalmology exam[l]	X	as clinically indicated[k]							
Visual acuity exam[k]	X	X		X	X		X	X	
Adverse event evaluation		X----------X						X	X[i]
Myeloma disease assessment[c] (section 11.2.1)	X	Assessments are repeated every 4 weeks. Documentation must be provided for patients removed from study for progressive disease.						X	

Radiologic evaluation[d]	X	Radiologic measurements, if indicated, for assessment of extramedullary disease should be performed every *12* weeks or upon clinical suspicion of progressive disease.						X	
B-HCG[e]	X	X						X	
Glycosulated Hemoglobin (HbA1c)	X				X				
PT/INR & PTT	X	X			X				
Urinalysis	X	X	X	X	X	X	X	X	
Skeletal Survey[g]	X								
Survival Follow-up									X
Correlative studies[h]: Peripheral blood and BM aspirate	X	On Day -2 to 1 of Cycle 2, 2-4 h after dosing with trametinib AND at progression And peripheral blood sample every even cycle for biomarker positive patients only			On Day -2 to 1 of Cycle 2, 2-4 h after dosing with trametinib and GSK2141795 AND at progression And peripheral blood sample every even cycle for biomarker positive patients only				

A. *[Trametinib]*: *2 mg daily of a 28 day cycle*
A* Trametinib 1.5 mg daily of a 28 day cycle (when used in combination with GSK2141795)
B. *[*GSK2141795*]*: *50 mg daily of a 28 day cycle*

a. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, fasting serum glucose. Weight and serum creatinine will be used to calculate creatinine clearance (eGFR and eCCr). Also see protocol guidelines for patient management and reporting of elevated liver function tests.

b. A single 12-lead ECG should be performed at screening and on the indicated visits. The QT interval corrected for heart rate should be calculated uing the Bazett's formula. (QT_b=QT/√RR)

c. Myeloma lab tests: ß2Microglobulin (collected at screening only); serum immunoelectrophoresis, immunoglobulin assay, M band confirmation by immunofixation and quantitation by SPEP, free light chain and 24 hour urine collection for Bence Jones protein to be performed at baseline prior to study, prior to each cycle thereafter and at time of study discontinuation (if last tests were > 4 weeks). FreeLyte test should occur if indicated by the Investigator. Not all tests may be required at each assessment time point. Tests can be done up to 7 days prior to day 1 of each cycle.

d. Radiological assessment for clinically suspected extramedullary disease should be performed prior to study (28 days) and every 12 weeks or upon clinical suspicion of progressive disease. This may include CT scan of the abdomen/pelvis, CT or x-ray of the chest, or ultrasound of the liver/spleen or abdomen. To ensure comparability, the baseline radiographs/scans and subsequent radiographs/scans to assess response should be performed preferably using identical techniques. The same method, radiological or physical, should be employed and assessed by the same individual on each occasion if possible.

e. Serum pregnancy test (women of childbearing potential).

g. Skeletal survey (including skull, all long bones, pelvis and chest) required if previous survey >12 weeks from study entry and at any time when clinically indicated.

h. Details on collection of samples, handling and shipping are provided in the Study Lab Manual. The patient may be dosed prior to study visit on cycle 2 day 1 (of single agent trametinib) and cycle 2 day 1 (of combination) to facilitate 2-4 h waiting for bone marrow aspiration. Baseline correlatives can be > 4 weeks prior to start of protocol therapy providing collection is after informed consent.

i. Refer to section 5.4

j. TSH testing to be done at the beginning of every 4th cycle

k. Snellen Chart and Visual Field Testing. If results of visual testing are abnormal the patient will be referred for an urgent full ophthalmologic exam

l. The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy.

m. To be performed if available at the treating institution.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors N/A

11.2 Antitumor Effect – Hematologic Tumors

11.2.1 Methods for Evaluation of Measurable Disease

Measurable disease. Measurable disease is defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to enrollment):

1. Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
2. Urine M-protein ≥ 200 mg/24 h
3. Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
4. Biopsy proven plasmacytoma (should be measured within 28 days of first study drug administration). Prior biopsy is acceptable.
5. If the serum protein electrophoresis is unreliable for routine M-protein measurement, quantitative immunoglobulin levels on nephrolometry or turbidometry will be followed.

Patients will be evaluated under local Investigator review for disease response according to the International Myeloma Working Group (IMWG) uniform response criteria (see 11.2.2; Rajkumar 2011).

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit)				
On Study Baseline Value	**SPEP**	**24 hr UPEP**	**Ig FLC**	**Plasmacytoma assessment**
Serum M-spike ≥ 0.5 g/dl, and urine M-spike ≥ 200 mg/24 hrs	X	X		
Serum M-spike ≥ 0.5 g/dl, but urine M-spike < 200 mg/24 hrs	X			
Serum M-spike < 0.5 g/dl, and urine M-spike ≥ 200 mg/24 hrs		X		
Serum M-spike < 0.5 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Plasmacytoma				X[a]
Immunofixation studies of both serum and urine are required to document CR regardless of registration values, and in addition **FLC** measurement and **BM immunophenotyping** is required to document sCR. [a] Complete evaluations done at baseline with same technique Q 12 weeks.				

Listed above are the minimal required tests to assess response based on the characteristics of disease at study initiation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document or confirm CR or sCR, except for patients with evaluable disease **only**, where BM assessment is required to document all response categories including progression. However, a second confirmatory BM is **not** required to confirm response.
- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.
- Progression does not require confirmation, but treating physician may continue an additional cycle to confirm progression if clinically indicated.

Bone progression: Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Principal Investigator before removing the patient from the study.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.2.2 Response Criteria

International Myeloma Working Group Response Criteria (Rajkumar *et al.,* 2011)
Response categories include sCR, CR, nCR, VGPR, PR, SD, and PD. In addition, minor response (MR) will be evaluated as an alternate response (see Section 11.3 for definition).

Response	*IMWG criteria*
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone BM by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in BM. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	1. 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the

	difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline BM plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	2. Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease	3. Increase of ≥ 25% from lowest response value in any one of the following: 1. Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or 2. Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or 3. Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL 4. Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) 5. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas 6. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All relapse categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. BM assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD: Clarified that BM criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. The 25% increase refers to M protein, FLC, and BM results, and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

11.3 Other Response Parameters

Additional response criteria for specific disease states:

Minor response in patients with relapsed and refractory myeloma adapted from the EMBT criteria[3]	≥ 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs.

	In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Immunophenotypic CR	Stringent CR plus Absence of phenotypic abarrent PC (clonal) in BM with a minimum of one million of total BM cells analyzed by miltiparamtric flow cytometry (with ≥4 colors)
Molecular CR	Stringent CR plus negative ASO-PCR (sensitivity 10^{-5})
Near Complete Response (adapted from the EMBT criteria [3])	Patients, in whom all criteria for a CR are satisfied with exception of a positive or an unconfirmed immunofixation result, will be considered a near CR (nCR).

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for entering their data into the Medidata Rave system and submitting copies of their source notes to the Central Office / Coordinating Centre within 3 weeks of the end of cycle. Please refer to APPENDIX D DATA MANAGEMENT GUIDELINES, Data Management Guidelines, for further details regarding data submission requirements.

The Central Office / Coordinating Centre is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in APPENDIX B CTEP MULTICENTER GUIDELINES

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in

any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a multi-center, open-label, non-randomized, two stage, phase II study of trametinib in patients with relapsed or refractory MM. BM samples from patients will be analyzed for NRAS, KRAS, BRAF mutations (next generation sequencing) at baseline visit. Patients will be statified into one of two study groups:

- Biomarker positive (NRAS, KRAS, BRAF mutated as defined in Appendix F)
- Biomarker negative (without NRAS, KRAS, BRAF mutation)

Patients will be independently recruited into either of the two groups based on biomarker positivity.

This study will use a two-stage design for both patient groups. Each group will enroll 12 patients in the first stage and an additional 25 patients in the second stage, if the pre-determined response criteria are met during the first stage. The target enrollment is a minimum of 24 evaluable subjects and a maximum number of 74 if both groups accrue to the second stage.
Individual patients will receive a minimum of 2 cycles and may remain on treatment as long as there is no evidence of disease progression or unacceptable toxicity or patient/physician decision to discontinue. As a secondary objective, patients who develop progressive disease on trametinib monotherapy or achieve less then a PR after 4 cycles of treatment will have the option to continue on GSK2141795 supplemented trametinib regimen. The dosing of trametinib and GSK2141795 will be according to the recommended 1.5 mg trametinib and 50 mg GSK2141795 daily dosing schedule. The M-protein level at the time of addition of GSK2141795 will be considered the new baseline, and the patients will be allowed to continue the new treatment schedule until further progression, toxicity, or patient/physician decision to discontinue.

The UHN Data Safety and Monitoring Board (DSMB) will evaluate the safety of the trial after completion of enrollment of the first 24 patients and/or biannually during phase II. If greater than 20% of subjects experience grade $\underline{4}$ diarrhea or rash despite optimal management or if greater then 10% subjects experience RPED or RVO or $\underline{\geq}$ 3 pneumonitis, a detailed review of these toxicities will be performed by an independent safety committee to determine whether the trial should be stopped.

The primary objective is to evaluate the antitumor activity of trametinib determined by overall response rate (ORR), in groups of patients with relapse or refractory multiple myeloma that are:

- Biomarker positive (NRAS, KRAS, BRAF mutated as defined Appendix F)
- Biomarker negative (without NRAS, KRAS, BRAF mutation)

The endpoint for the primary objective, ORR, is evidenced by confirmed response rate, defined as number of patients with partial response or better by IMWG criteria divided by the number of patients in the applicable group (biomarker positive or negative). All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible (see section 13.5.2). The patient will be classified as having had a response if he/she has a confirmed response per the definitions in section 11.2.2. (i.e., a stringent complete response, or complete response or near complete response or very good partial response or partial response noted as the objective status of two consecutive assessments). The rate of minor response (MR) and progressive disease (PD) will also be observed.

13.2 Sample Size/Accrual Rate

A two-stage design will be used for each group to test the null hypothesis that the extended ORR is 5% or less, versus the alternative hypothesis that the extended ORR is greater then 5% using a one-sided test with a 10% level of significance and 90% power at the alternative extended ORR of 20%. The null hypothesis of extended ORR=0.05 and the alternative extended ORR=0.20 are chosen with reference to response rate with trametinib in BRAF mutated melanoma of 22% (Flaherty *et al.,* 2012) and the response rates of single agent carfilzomib (17%) (Jagannath *et al.,* 2012) and pomalidomide (7%) (Dimopoulos *et al,* 2012). The design is standard for such single-arm Phase II studies and appropriately minimizes the number of expected study participants when the experimental treatment is truly ineffective.

The target enrollment therefore is a minimum of 24 evaluable subjects and a maximum of 74 if both groups (biomarker positive and biomarker negative) accrue to the second stage. After testing the drug on 12 patients in each group, the trial will go to the second stage if one or more subjects respond. If the trial goes to the second stage, a total of 37 patients will be studied. If the total number of responding is more than or equal to to 4, the drug is accepted. The same design as above will apply to both strata. The maximum number of this study would be 74 patients for both strata. The distribution of PFS and DOR will be summarized for each cohort using the Kaplan-Meier method. For each of these endpoints, patients will be right-censored at the date at which they were last known not to have the corresponding event.

Subjects who receive at least one dose of trametinib will be evaluable for safety. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary. The results will be tabulated to examine their frequency, organ systems affected, and relationship to study treatment. The results of laboratory assessments will be evaluated similarly. Interim safety data will be examined on an ongoing basis to ensure subject safety.

Exploratory analyses of the association of response with pharmacogenomic and pharmacodynamic will be descriptively summarized. Overall, given the limited sample size these analyses will be largely hypothesis-generating.

13.3 Stratification Factors

BM samples from patients will be analyzed for NRAS, KRAS, BRAF mutations (next generation sequening) at baseline visit. Patients will be stratified into one of two study groups as strategy for biomarker-based patient enrichment:

- Biomarker positive (NRAS, KRAS, BRAF mutated as defined Appendix F)
- Biomarker negative (without NRAS, KRAS, BRAF mutation)

Patients in both groups will receive 2.0 mg daily oral trametininb. Each group will enroll 12 patients in the first stage and an additional 25 patients in the second stage, if the pre-determined response criteria are met during the first phase.

13.4 Analysis of Secondary Endpoints

The secondary objectives are to:

- To evaluate progression free survival (PFS) and duration of response (DOR) in the two stratified groups
- To document ORR after the addition of GSK2141795 to trametinib in patients who have developed progressive disease or have achieved less then a partial response (PR) after 4 cycles of treatment
- To evaluate PFS and DOR in patients receiving trametinib plus GSK2141795
- To evaluate the safety profile of trametinib with and without GSK2141795

The endpoints for secondary objectives**,** ORR is defined in sections 13.1 and 13.5.2 and will employ the M-protein level at the time of addition of GSK2141795 as the new baseline for response assessment.

Safety analyses will review adverse events, electrocardiogram results, laboratory tests (hematology, clinical chemistry, and coagulation test), vital signs and physical examinations. Any patient who receives any amount of the study drug will be evaluated for toxicity. Safety will be measured in terms of type, frequency and severity of adverse event reactions reported according to CTCAE v4.0.

PFS will be evaluated as defined by the time from the date of start of treatment to the date of documented progression (based on IMWG criteria) or death due to any cause. For patients who are not known to have died and who do not have objective evidence of tumor progression, and who are either removed from study treatment or who are given antitumor treatment other than the assigned study treatment, PFS will be censored at the last complete disease assessment. Patients who complete the study and have not progressed at the cut-off date for final analysis will be censored at the last complete disease assessment. Patients with two or more missing assessments immediately prior to the next visit with a documented progression will be censored for PFS at the last assessment with documentation of no progression.

The DOR is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented or to death due to multiple myeloma (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). For patients with responding tumors who do not have objective evidence of tumor progression and are either removed from study treatment or who are given antitumor treatment other than the study treatment or who die from non-disease causes, duration of response will be censored.

The exploratory objectives are:

- To explore the relationship between clinical response and pharmacodynamic (PD) markers
- To explore the relationship between MAF expression and chromosomal abnormalities as determined by qPCR and FISH, respectively, and clinical response
- To explore the role of integrin β7 as a biomarker of MAF expression
- To explore the relationship between objective response as well as progressive disease and the tumor mutational profile
- To explore mechanism of PI3K/AKT and RAS-MEK-ERK activation and correlate these with clinical response and PD markers
- To explore the feasibility extracting cfDNA from peripheral blood and to detect RAS and RAF mutaitons using cfDNA

The activation state of the PI3K/AKT, RAS-MEK-ERK and additional signaling pathways pre and post-treatment will be determined by phospho-flow cytometry and RPPA and correlated with clinical response.

The level of MAF expression at baseline will be determined by qPCR. The cutoff value for the qPCR assay will be determined by calculating the median ratio and range relative copy number for 20 myeloma cell lines that are MAF positive (t(14;16) and t(4:14) cell lines) and 20 cell lines that are negative. Results of the PCR reactions will be compared to Western blot to confirm MAF expression and determine the sensitivity and specificity of the assay and its cutoff. To determine the performance of the assay in the clinical samples we will compare results obtained by qPCR to FISH data Although this assessment will be done retrospectively, the data will be available for inerim analysis for correlation with clinical response. If the data indicate that MAF may be a predictive biomarker the protocol may be modified to enrich for this subgroup of patients.

The cell surface expression of integrin β7 will be determined by flow cytometry on CD138 positive myeloma cells derived from screening BM samples. Correlation with MAF expression will be determined.

Next generation sequencing (Truseq or Trusight) for mutational profiling will be performed on samples obtained at screening and at progression to identify mutations that are associated with response and acquired resistance to trametinib. Although this assessment will be done retrospectively, the data will be available for inerim analysis for correlation with clinical response. If the data indicate that a particular mutation and molecular pathway may be a predictive a predictive biomarker the protocol may be modified to enrich for this subgroup of patients.

The effect of trametinib on PI3K/AKT and RAS-MEK-ERK with and without the addition of

GSK2141795 evaluated by phospho-flow cytometry will be used to determine whether escape mechanisms are ERK-dependent or ERK-independent and driven by PI3K/AKT signaling. cfDNA will be extracted from peripheral blood samples. Ultra-deep sequencing will be performed on cfDNA to assess the feasibility of detecting mutations of NRAS, KRAS and BRAF from peripheral blood samples.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evalable for toxicity from the time of their first treatment with trametinib. Toxicity analyses will review adverse events, electrocardiogram results, laboratory tests (hematology, clinical chemistry, and coagulation test), vital signs and physical examinations. Safety will be measured in terms of type, frequency and severity of adverse event reactions reported according to CTCAE v4.0.

13.5.2 Evaluation of Response

All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) stringent complete response, 2) complete response, 3) very good partial response 4) partial response, 5) minimal response 6) stable disease, 7) progressive disease, 8) early death from malignant disease, 9) early death from toxicity, 10) early death because of other cause, or 11) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 7-10 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions on treatment efficacy will be based on all eligible patients. Sub-analyses for objective response rate will be performed on all patients meeting the eligibility criteria, who have signed a consent form, and have begun study drug treatment, and had at least one follow-up assessment or progressive disease. This analysis will clearly report the reason for exclusion that may be based on major protocol deviations such as early death due to other reasons, early discontinuation of treatment, major protocol violations, etc. Further, the 95% confidence intervals will be provided.

REFERENCES

Annunziata C.M., Hernandez L., Davis R.E., et al. (2011) A mechanistic rationale for MEK inhibitor therapy in myeloma based on blockade of MAF oncogene expression. . *Blood.* 117(8):2396-404.

Balagula, Y., K. Barth Huston, K.J. Busam, *et al.* (2010). Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). *Invest New Drugs.* 29:1114-1121.

Bekaii-Saab, T., M.A. Phelps, X. Li, *et al.* (2011). Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *J Clin Oncol.* 29:2357-2363.

Bendell, J., P. LoRusso, E. Kwak, *et al.* (2011). Clinical combination of the MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941: A first-in-human phase Ib study in patients with advanced solid tumors. *AACR Meeting Abstracts.* Abstract LB-89.

Billadeau D., Jelinek D.F., Shah N., LeBien T.W., Van Ness. B. (1995). Introduction of an activated N-ras oncogene alters the growth characteristics of the interleukin 6-dependent myeloma cell line ANBL6. *Cancer Res.* 55(16):3640-6.

Borthakur, G., J.M. Foran, T. Kadia, *et al.* (2010). GSK1120212, a MEK1/MEK2 inhibitor, demonstrates acceptable tolerability and preliminary activity in a dose rising trial In subjects with AML and other hematologic malignancies. *Blood (ASH Annual Meeting Abstracts).* 116:Abstract 3281.

Chapman MM, Lawrence M.S., Keats J.J. et al. (2011). Initial genome sequencing and analysis of multiple myeloma. *Nature.* 471(7339):467-472.

Chow S., Hedley D., Shankey T.V. (2008). Whole blood processing for measurement of signaling proteins by flow cytometry. *Curr Protoc Cytom.* Chapter 9:Unit 9.27.

Corradini P., Ladetto M., Inghirami G., Boccadoro M., Pileri A. (1994). N- and K-ras oncogenes in plasma cell dyscrasias. *Oncogene*. 21(57):8769-75.

Dalton W.S., Bergsagel P.L., Kuehl W.M., Anderson K.C., Harousseau J.L (2001). Multiple myeloma. *Hematology Am Soc Hematol Educ Program*.157-77.

De P., Dey N., Terakedis B., et al. (2013), An integrin-targeted, pan-isoform, phosphoinositide-3 kinase inhibitor, SF1126, has activity against multiple myeloma in vivo. *Cancer Chemother Pharmacol.* 71(4):867-81.

Dimpoulos M, Spencer A, Attal M et al (2007). Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2007;357:2123-32.

Dimopoulos M.A., Lacy M.Q., Moreau P., et al. (2012) Pomalidomide in Combination with

Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study. *Blood (ASH Annual Meeting Abstracts).* 120:Abstract LBA-6.

Ebi H,, R.B. Corcoran, A. Singh, *et al.* (2011). Receptor tyrosine kinases exert dominant control over PI3K signaling in human KRAS mutant colorectal cancers. *J Clin Invest.* 121:4311-4321.

Engelman, J.A., L. Chen, X. Tan, *et al.* (2008). Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med.* 14:1351-1356.

Flaherty, K.T., C. Robert, P. Hersey, *et al.* (2012). Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 367:107-114.

Gilmartin, A.G., M.R. Bleam, A. Groy, *et al.* (2011). GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. *Clin Cancer Res.* 17:989-1000.

Gopal, Y.N., W. Deng, S.E. Woodman, *et al.* (2010). Basal and treatment-induced activation of AKT mediates resistance to cell death by AZD6244 (ARRY-142886) in Braf-mutant human cutaneous melanoma cells. *Cancer Res.* 70:8736-8747.

Hervé, A.L., Florence M., Philippe M., et al. (2011). Molecular heterogeneity of multiple myeloma: pathogenesis, prognosis, and therapeutic implications. *J Clin Oncol.* .29(14):1893-7.

Hoeflich, K.P., C. O'Brien C, Z. Boyd, *et al.* (2009). In vivo antitumor activity of MEK and phosphatidylinositol 3-kinase inhibitors in basal-like breast cancer models. *Clin Cancer Res.* 15:4649-4664.

Holkova, B., Badros, A.F., Geller R., et al. (2011) A Phase II Study of the MEK 1/2 Inhibitor AZD6244 (Selumetinib, ARRY-142866) in Relapsed or Refractory Multiple Myeloma. *Blood (ASH Annual Meeting Abstracts).* 118:Abstract 2931,

Howlader N., Noone A.M., Krapcho M., Garshell J, et al. (2013). *SEER Cancer Statistics Review, 1975-2010*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013.

Hurt E.M., Wiestner A., Rosenwald A., et al. (2004). Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. *Cancer Cell.* 5(2):191-9.

Infante, J.R., Fecher L.A., Nallapareddy, S., *et al.* (2010). Safety and efficacy results from the first-in-human study of the oral MEK 1/2 inhibitor GSK1120212. *J Clin Oncol.* 28:Abstract 2503.

Investigator's Brochure. (2012a). GSK1120212. *GlaxoSmithKline*. Version 04. September 5, 2012.

Investigator's Brochure. (2012b). GSK2118436. *GlaxoSmithKline*. Version 04. May 15, 2012.

Jagannath, S., ViJ, R., Stewart, A.K. et al. (2012) An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 12(5):310-8.

Kirkwood, J.M., L. Bastholt, C. Robert, *et al.* (2012). Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. *Clin Cancer Res.* 18:555-567.

Kurzrock, R., A. Patnaik, L. Rosenstein, *et al.* (2011). Phase I dose-escalation of the oral MEK1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral AKT inhibitor GSK2141795 (GSK795). *J Clin Oncol.* 29:Abstract 3085.

Lacouture, M.E., M.J. Anadkat, R.J. Bensadoun, *et al.* (2011). Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 19:1079-1095.

Ladevaia, S., Lu, Y., Morales, F.,C,, Mills, G.B., Ram, P.T. (2010). Identification of Optimal Drug Combinations Targeting Cellular Networks: Integrating Phospho-Proteomics and Computational Network Analysis. *Cancer Res.* 70(17); 1–11.

Labauch J.P., Mitsiades C.S., Mahindra A, (2009). Novel therapies in the treatment of multiple myeloma. *J Natl Compr Canc Netw.* 7(9):947-60.

Mao X., Stewart A.K., Hurren R., et al. (2007) A chemical biology screen identifies glucocorticoids that regulate c-maf expression by increasing its proteasomal degradation through up-regulation of ubiquitin. *Blood.* 110(12):4047-54.

McCubrey J.A., Steelman L.S., Chappell W.H., et al. (1994), Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Leuk Lymphoma.* 5(1-2):17-20.

Messersmith, W.A., G.S. Falchook, L.A. Fecher, *et al.* (2011). Clinical activity of the oral MEK1/MEK2 inhibitor GSK1120212 in pancreatic and colorectal cancer. *J Clin Oncol.* 29:Abstract 246.

Morgan G.J., Walker B.A., Davies F.E. (2012). The genetic architecture of multiple myeloma. *Nat Rev Cancer*. 12(5):335-48.

Munshi N.C., Anderson K.C.,Bergsagel P.L., et al. (2011). Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood.* 117(18):4696-700.

.

Peterson T.R., Laplante M., Thoreen C.C., et al. (2009). DEPTOR is an mTOR inhibitor frequently overexpressed in multiple myeloma cells and required for their survival. *Cell*. 137(5):873-86.

Raab M.S., Podar K., Breitkreutz I., Richardson P.G., Anderson K.C. (2009). Multiple myeloma. *Lancet.* 374(9686):324-39.

Rajkumar, S.V., Jacobus, S., Callander, N.S., et al. (2010). Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as intial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. *Lancel Oncol.* 11:29-37.

Rajkumar S.V., Harousseau J.-L., Durie B., et al. (2011) Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood, 117(18):4691-5.

Richardson, P.G., B. Barlogie, J. Berenson et al. (2003) A phase 2 study of BZ in relapsed, refractory myeloma. *N Engl J Med* 348, 2609-17.

Rowley M., Van Ness B. (2002). Activation of N-ras and K-ras induced by interleukin-6 in a myeloma cell line: implications for disease progression and therapeutic response. *Oncogene*. 21(57):8769-75.

Santarpia L., Lippman S.M., El-Naggar A.K. (2012). Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opin Ther Targets.* 16(1):103-19.

Steinbrunn T., Stühmer T., Gattenlöhner S, et al. (2011). Mutated RAS and constitutively activated Akt delineate distinct oncogenic pathways, which independently contribute to multiple myeloma cell survival. *Blood.* 117(6):1998-2004.

Tartaglia M, Gelb BD, Zenker M. (2011). Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab.* 25(1):161-79.

Thierry AR, Mouliere F, Messaoudi SE et al. (2014). Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. *Nature Medicine*. 20:410-436.Tolcher, A.W., J.C. Bendell, A. Patnaik, *et al.* (2011). A phase Ib study of the MEK inhibitor GSK1120212 combined with gemcitabine in patients with solid tumors: Interim results. *J Clin Oncol.* 29:Abstract 278.

Tong F.K., Chow S., Hedley D. (2006). Pharmacodynamic monitoring of BAY 43-9006 (Sorafenib) in phase I clinical trials involving solid tumor and AML/MDS patients, using flow cytometry to monitor activation of the ERK pathway in peripheral blood cells. *Cytometry B Clin Cytom*. 70(3):107-14.

Weber, J.S., K.T. Flaherty, J.R. Infante, *et al.* (2012). Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naïve metastatic melanoma. *J Clin Oncol.* 30:Abstract 8510.

Weiss B.M., Kuehl W.M. (2010). Advances in understanding monoclonal gammopathy of undetermined significance as a precursor of multiple myeloma. *Expert Rev Hematol.* 3(2):165-74.

Yamaguchi, T., R. Kakefuda, N. Tajima, *et al.* (2011). Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo. *Int J Oncol.* 39:23-31.

Zingone, A., N. Korde, J. Chen, *et al.* (2011). Molecular characterization and clinical correlations of MEK1/2 inhibition (AZD6244) in relapse or refractory multiple myeloma: analysis from a phase II study. *Blood (ASH Annual Meeting Abstracts).* 118:Abstract 306.

Zöllinger A., Stühmer T., Chatterjee M., et al. (2008). Combined functional and molecular analysis of tumor cell signaling defines 2 distinct myeloma subgroups: Akt-dependent and Akt-independent multiple myeloma. *Blood.* 112(8):3403-11.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent **trametinib dimethyl sulfoxide and/or GSK2141795.** *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Trametinib dimethyl sulfoxide or GSK2141795 interact with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Trametinib dimethyl sulfoxide or GSK2141795 interact with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question are ***CYP 3A4 and 2C8***. CYP 3A4 is responsible for breaking down trametinib dimethyl sulfoxide in your liver. Trametinib dimethyl sulfoxide or GSK2141795 may prevent other drugs from being broken down in your liver by CYP 2C8
- Trametinib dimethyl sulfoxide or GSK2141795 must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the activity of CYP 3A4 ("inducers") could reduce the effectiveness of trametinib dimethyl sulfoxide or GSK2141795, while substances that decrease that enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
    - Trametinib dimethyl sulfoxide or GSK2141795 is considered an "inhibitor" of CYP 2C8, meaning that it can affect the levels of other drugs that are processed by that enzyme. This can lead to harmful side effects and/or reduce the

effectiveness of those medications.

- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors" of **CYP 3A4** or highly sensitive substrates of CYP3A4 or **CYP 2C8**.
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking trametinib dimethyl sulfoxide.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent trametinib dimethyl sulfoxide and GSK2141795**.** This clinical trial is sponsored by the NCI. Trametinib dimethyl sulfoxide interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Trametinib dimethyl sulfoxide interacts with a specific liver enzyme called **CYP 3A4 and 2C8**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4 and 2C8**."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis//table.aspx for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____**.**

APPENDIX D DATA MANAGEMENT GUIDELINES

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the PMH Phase 2 Consortium Central Office. The site will be required to complete a paper Eligibility Checklist case report form (CRF) at the time of patient registration. All other data will be collected on electronic case report forms (eCRFs) in the Medidata Rave system. Site staff access to Medidata Rave will be initiated at the time of site activation. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline eCRFs	Within 3 weeks of on study date
On Treatment (Cycle) eCRFs	Within 3 weeks of each visit
Off Treatment eCRFs	Within 3 weeks of the patient coming off-study
Short Follow-up eCRFs	Within 3 weeks of the patient coming to clinic.
Final eCRFs	Within 3 weeks from the follow-up period being complete or of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to CTEP-AERS guidelines

Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs will be completed according to the schedule noted above and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted to the PMHC Phase 2 Consortium Central Office for review. All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number.

eCRF completion guidelines are available for all sites.

Monitoring

Central data monitoring will take place throughout the trial at the Central Office. On-site monitoring will be performed once a year at participating sites during which a subset of PMHC

studies will be picked for on-site monitoring.

Data in the Medidata Rave eCRFs will be monitored on a regular basis and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site prior to the quarterly submission of data to CDUS.

Patient Registration

- Refer to section 4 of the protocol

Data Safety

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent.

Regulatory Requirements

- Please submit all required documents to the PMH Phase 2 Consortium Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- All investigators must have a current NCI investigator number on file with the PMH Phase 2 Consortium Central Office.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the PMH Phase 2 Consortium Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergoes such training.
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- OPRR assurance numbers for each institution are required
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the PMH Phase 2 Consortium Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the PMH Phase 2 Consortium Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to PMHC
- Continuing approval will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

APPENDIX E DIARY CARD

INSTRUCTIONS – **Trametinib and GSK2141795 Combination Therapy**

1. You will take ___ 0.5 mg trametinib tablets (___ mg total dose) once a day on an empty stomach; either 1 hour before or 2 hours after a meal.
2. ___ 25 mg GSK2141795 capsules (___ mg total dose) are taken once a day, fasting 1 hour after a small

INSTRUCTIONS – **Trametinib Monotherapy**

1. You will take **2 mg** trametinib tablets or **1.5 mg** trametinib once a day. Trametinib tablets must be taken on an empty stomach either 1 hour before or 2 hours after a meal.
2. Swallow each tablet whole. Do not crush or chew the tablets.
3. Record the date you took the Trametinib and indicate time that the dose was taken.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form at each clinic visit.
6. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.
7. If you miss any of the doses or you vomit one of the tablets, do not take any extra dose, and call your study doctor.

Day	Date - Time	Trametinib Dose	Comments
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

Physician's Office will complete this section:
The above information has been reviewed with the patient:
Patient Name:_____
Physician/Nurse Signature _____ Date _____

snack **and** 2 hours before the next meal.

Eat a small snack followed by 60 minutes of fasting prior to taking GSK2141795 capsules. Water is allowed during this fasting period. If possible, take each capsule approximately 5 minutes apart with divided amounts of fluid (4-8oz with each capsule for a total of at least 12 oz).For example: Eat breakfast. Take GSK2141795 one hour after eating, and then wait 2 hours. Take trametinib, and wait one hour before eating the next meal.

3. Swallow each capsule whole. Do not crush or chew the capsules.
4. Stay upright (standing or sitting up) for at least 30 minutes after taking the last GSK2141795 capsule for each dose.
5. Fast for 2 hours (water is allowed) after taking the last GSK2141795 capsule for each dose.
6. Record the date you took Trametinib/ GSK2141795, and indicate the time that the dose was taken.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please bring this form at each clinic visit.
9. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.
10. If you miss any of the doses or you vomit one of the tablets or capsules, do not take any extra dose, and call your study doctor.

Day	Date - Time	Trametinib Dose	GSK2141795 Dose	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Physician's Office will complete this section:
The above information has been reviewed with the patient:
Patient Name:_____
Physician/Nurse Signature _____ Date _____

APPENDIX F MUTATIONAL PROFILING

TABLE 1: TruSeq Amplicon Cancer Panel

ABL1	*EGFR*	*GNAS*	*MLH1*	*RET*
AKT1	*ERBB2*	*HNF1A*	*MPL*	*SMAD4*
ALK	*ERBB4*	*HRAS*	*NOTCH1*	*SMARCB1*
APC	*FBXW7*	*IDH1*	*NPM1*	*SMO*
ATM	*FGFR1*	*JAK2*	*NRAS*	*SRC*
BRAF	*FGFR2*	*JAK3*	*PDGFRA*	*STK11*
CDH1	*FGFR3*	*KDR*	*PIK3CA*	*TP53*
CDKN2A	*FLT3*	*KIT*	*PTEN*	*VHL*
CSF1R	*GNA11*	*KRAS*	*PTPN11*	
CTNNB1	*GNAQ*	*MET*	*RB1*	

Cancer-related genes represented in the TSACP. For a full list of target regions, see the manifest file[1] (MyIllumina login required).

TABLE 2: TruSight Cancer Panel

AKT1	*EGFR*	*GNAS*	*NRAS*	*STK11*
ALK	*ERBB2*	*KIT*	*PDGFRA*	*TP53*
APC	*FBXW7*	*KRAS*	*PIK3CA*	
BRAF	*FGFR2*	*MAP2K1*	*PTEN*	
CDH1	*FOXL2*	*MET*	*SMAD4*	
CTNNB1	*GNAQ*	*MSH6*	*SRC*	

Genes selected from NCCN[1] and CAP[2] guidelines, late-stage clinical trials[3], and relevant publications for lung, colon, melanoma, gastric and ovarian[4].

TABLE 3: KRAS, NRAS, BRAF Mutation List

KRAS	**exon 2**	**exon 3**	**exon 4**	**exon 5**
TruSeq	Met1_Glu31	Asp38_Gln70	Arg97_Gln150	N/A
TruSight	Met1_Glu37	Asp38_Arg97	Arg97_Gln150	Gly151_189X

NRAS	**exon 2**	**exon 3**	**exon 4**	**exon 5**
TruSeq	Met1_Asn26	Asp38_Gln70	N/A	N/A
TruSight	Met1_Glu31	Asp38_Arg97	Arg97_Gln150	Gly151_190X

BRAF	**exon 11**	**exon 15**
TruSeq	Lys439_His477	Asn581_Leu613
TruSight	Lys439_His477	Asn581_Trp619